EXHIBIT 183

From: BENES, CHARLES O. [PHR/1825]
Sent: Wednesday, December 13, 2000 10:36 PM
To: COUGHLIN, OLIVIA A. [PHR/1825]
Cc: BENES, CHARLES O. [PHR/1825]
Subject: CBX-0014929_ FW: CLASS Briefing Document

CBX-0014930_
CLASSBriefingDoc_..

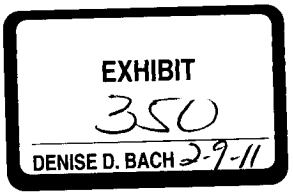
Olivia:
CLASS Briefing Document for your review.
Please return comments to Jim lefkowith by noon on Mon, 18 Dec 2000.

Electronic copies have also been eMailed to the folks below, plus W. Begley and P. Isakson.
J. Lefkowith send advance copy to M. Tansey and L. Kundel.
Hard copies were FEDEXED on 12/13 to: G. Ando, P. Needleman, R. Garutti, C. Cox, N. Wolf, F. Arellano.
This covers all the folks that Fred said should review the document.
Chuck

-----Original Message-----
From: LEFKOWITH, JAMES B. [PHR/1825]
Sent: Tuesday, December 12, 2000 6:01 PM
To: ZHAO, WILLIAM W [PHR/1825]; MAURATH, CLEMENT [PHR/1825]; BURR, AIMEE M. [PHR/1825]; KENT, JEFFREY D [PHR/1825]; RIDGE, NANCY J [PHR/1825]; JAIN, RITA I [R&D/1825]; WOODS, EMMETT M. [PHR/1825]; CALLISON, DAVID A. [PHR/1825]; KATZ, TERESA K [PHR/1825]; YANG, TERESA C [PHR/1825]; PAPERIELLO, BEVERLY A [PHR/1825]; KAISER, JUNE [PHR/1825]; BENES, CHARLES O. [PHR/1825]; VERBURG, KENNETH M [PHR/1825]; WAHBA, MONA M [PFIZER/Off-Site]
Subject: CLASS Briefing Document

To all-
Comments due by Monday.
JL

Mona-
Please circulate draft to all relevant parties in Pfizer and collate comments.
JL



CELECOXIB LONG-TERM ARTHRITIS SAFETY STUDY (CLASS)
ADVISORY COMMITTEE BRIEFING DOCUMENT

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1. ABSTRACT

Conventional nonsteroidal anti-inflammatory drugs (NSAIDS) are widely used to treat inflammatory diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA). Well-established limitations of NSAID therapy, however, include the risk of significant injury to the upper gastrointestinal (GI) tract due to inhibition of cyclooxygenase (COX), specifically the COX-1 isoform.

Celecoxib, a COX-2-specific inhibitor that spares COX-1 at therapeutic and supratherapeutic doses, is indicated for the relief of the signs and symptoms of OA and RA in adults. Data submitted with the original NDA establish that celecoxib is associated with a lower incidence of endoscopic ulcers and, in a meta-analysis of the database, fewer ulcer complications than conventional NSAIDs. The objective of the Celecoxib Long-term Arthritis Safety Study (CLASS) was to provide further evidence of the GI safety profile of celecoxib by determining whether celecoxib is associated with a lower incidence of significant upper GI toxic effects (ulcer complications and symptomatic ulcers) and other adverse effects compared to conventional NSAIDs in a double-blind, randomized, controlled trial.

In the CLASS trial, patients with OA or RA were randomly assigned to receive celecoxib 400 mg twice daily or a conventional NSAID comparator (ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily). The dose of celecoxib chosen was two- to four-fold greater than the maximum and recommended doses for the treatment of RA and OA, respectively, to rigorously assess the safety of celecoxib. Comparator NSAIDs were administered at commonly used doses for the OA and RA population. The trial was constructed to replicate clinical practice and employed nonrestrictive inclusion and exclusion criteria. Accordingly, aspirin use for cardiovascular prophylaxis ($\leq$325 mg per day) was permitted during the study. Outcome measures were the incidence of prospectively defined ulcer complications (bleeding, perforation, and obstruction; primary outcome) as well as symptomatic ulcers/ulcer complications combined and other adverse events. An evaluation of potential risk factors for GI toxicity was prespecified in the protocol to determine their impact on outcomes and to address sources of bias in the data.

A total of 8059 patients were enrolled into the study. Of these, 7968 patients received at least one dose of study medication, and 4573 patients received treatment for six months.

For all treated patients, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib versus comparator NSAIDs were 0.76% versus 1.45% (p=0.09) and 2.08% versus 3.54% (p=0.02), respectively. Consistent with the literature, aspirin was identified as an independent cause of ulcer complications. Thus, analysis was performed in the non-aspirin-taking cohort. For patients not taking aspirin, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers were 0.44% versus 1.27% (p=0.04) and 1.40% versus 2.91% (p=0.02), respectively.

Risk factor analysis identified risk factors for upper GI toxicity associated with conventional NSAIDs similar to those identified in previous studies. Analyses were performed specifically for the six-month treatment period to minimize bias due to the progressive depletion of susceptible patients in the NSAID treatment groups, that is, patients with two or more risk factors who were at highest risk for developing an ulcer complication.

The incidence rates of ulcer complications alone or combined with symptomatic ulcers associated with celecoxib were significantly lower than the incidence rates associated with ibuprofen, and numerically lower than the incidence rates associated with diclofenac. However, withdrawals due to GI intolerance were significantly greater in the diclofenac group than in the other treatment groups. Moreover, GI intolerance was identified as a risk factor for ulcer complications and symptomatic ulcers. Therefore, the greater withdrawal rate of patients with GI intolerance from the diclofenac cohort prematurely removed a high-risk group for ulcer complications and symptomatic ulcers from this treatment arm and biased the observed event rates. Statistical adjustment for this source of bias indicated that the observed rate of events in the diclofenac group were underestimates.

In the general safety assessments, the safety profile of supratherapeutic doses of celecoxib was generally the same as for therapeutic doses of celecoxib. No dose- or duration-dependent toxicities were observed with the exception of a higher incidence of nonserious rash. Of specific note, celecoxib was associated with a significantly lower incidence of chronic decreases in hematocrit and hemoglobin, presumably due to chronic GI blood loss, relative to comparator NSAIDs. In terms of renal safety, celecoxib was associated with a

significantly lower incidence of edema and hypertension relative to ibuprofen and a lower incidence of changes in BUN/creatinine relative to diclofenac. Celecoxib was also associated with a significantly lower incidence of clinically relevant changes in liver function tests compared to diclofenac. No difference in the incidence of thromboembolic cardiovascular events was seen between celecoxib and comparator NSAIDs regardless of aspirin use.

In order to further explore the safety profile of celecoxib, data from the long term open label safety trial (Study 024) and the first year of postmarketing surveillance were analyzed. In terms of GI toxicity, the ulcer complication rate from Study 024 was 0.23%, and the reporting rate of ulcer complications from postmarketing surveillance was <0.02%. These estimates are consistent with the incidence rates from the CLASS study. No dose- or duration-dependent toxicities have emerged from either Study 024 or postmarketing surveillance. No rare toxicities not noted in the product insert have been observed after the first year of marketing.

In sum, the CLASS study combined with the NDA, long-term open-label trial, and postmarketing surveillance support the contention that celecoxib is associated with a significantly lower incidence of clinically significant upper GI toxicity relative to conventional NSAIDs. Moreover, no safety issue has emerged with long term and widespread use to mitigate this safety advantage.

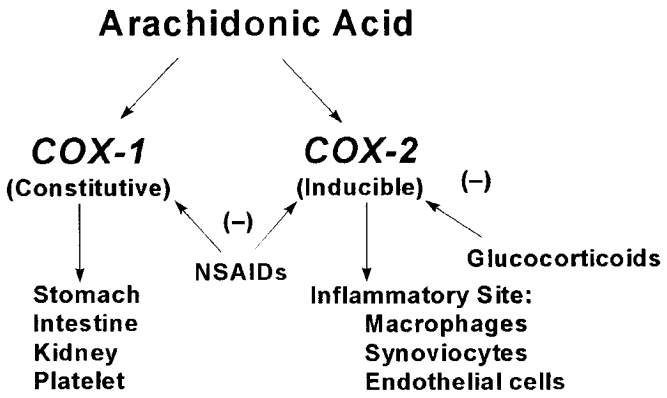
2. INTRODUCTION

2.1. Overview

Conventional NSAIDs are an important component of the standard of care for OA and RA. (1) These agents provide analgesic and anti-inflammatory effects via their inhibition of COX, the enzyme that catalyzes the conversion of arachidonic acid into prostaglandins and thromboxane, autacoids that mediate pain and inflammation. (2) Conventional NSAIDs as a class of drugs, however, exhibit a common adverse effect profile. Many of these adverse effects are mechanism-based and result from the inhibition of prostaglandins and thromboxane: specifically, GI toxicity, inhibition of platelet function, and renal dysfunction. Other common adverse effects of conventional NSAIDs are less clearly mechanism-based, and include effects such as GI intolerance, hepatotoxicity, and dermatologic reactions. (3)

Several years ago, two distinct isoforms of COX were identified and designated COX-1 and COX-2. COX-1 is constitutively expressed in most tissues throughout the body, including the GI tract, kidney, and platelets. COX-2 is normally found in very low amounts in healthy tissue but is rapidly and highly induced in inflamed tissues by inflammatory mediators (4) The therapeutic benefits of conventional NSAIDs are largely due to the inhibition of COX-2 at inflammatory sites, while the GI toxicity and platelet effects result from inhibition of COX-1. Because both COX-1 and COX-2 are expressed in the kidney, the mechanism of the renal effects of conventional NSAIDs is somewhat complex, but toxicity is in part COX-1-mediated. (5)

Figure 2.a. **Roles of COX-1 and COX-2 and Mechanism of Action of Conventional NSAIDs**



This advance in understanding of the roles of the COX isoforms led to the development of celecoxib, a specific COX-2 inhibitor. The rationale behind the development of celecoxib was to provide comparable therapeutic benefit to conventional NSAIDs via COX-2 inhibition, without the attendant COX-1-mediated toxicities inherent to the mechanism of conventional NSAIDs. The data submitted with the original celecoxib New Drug Application (NDA 20,998) demonstrated that celecoxib is safe and effective in treating the signs and symptoms of both OA and RA, as well as the potential safety advantage of celecoxib. (6-10) Specifically, celecoxib was shown to be associated with statistically significantly lower incidences of endoscopically detected gastroduodenal ulcers and fewer ulcer complications than conventional NSAIDs. In order to further establish the correlation between reduced ulcer incidences and a lowered number of associated ulcer complications, the CLASS trial was performed in a prospective, controlled, double-blind fashion to compare the incidence of clinically significant upper GI toxicity between celecoxib and comparator NSAIDs (diclofenac and ibuprofen) under clinical practice conditions. It is worth noting, however, that the prospective, controlled, double-blind study design is not impervious to bias relating to patient withdrawal, changes in clinical care patterns, and cotherapies.

This Briefing Document will review the CLASS study results in the context of the original NDA, the recently completed long-term safety trial (Study 024), and ongoing

postmarketing surveillance in order to provide a comprehensive and current review of the safety of celecoxib.

2.2. NSAID Toxicity

Conventional NSAIDs exhibit a number of mechanism-based toxicities derived from their inhibition of COX-1, the principal such toxicity being GI in nature. (11,12) Conventional NSAIDs cause symptomatic gastroduodenal ulcers and ulcer complications (upper GI bleeding, perforation, and obstruction) at a rate of two to four cases per 100 patient-years, the occurrence of ulcer complications alone being between one and two cases per 100 patient-years. (13,14) Ulcer complications specifically are a substantial source of conventional NSAID-associated morbidity and mortality, with an estimated 107,000 hospitalizations and 16,500 deaths attributable to this class of drugs annually in the United States. (14) The occurrence of ulcer complications is common to all conventional NSAIDs, is dose-dependent, and has been observed even in patients taking low-dose aspirin for cardiovascular prophylaxis. (15,16) The risk of conventional NSAID-associated ulcer complications also appears to remain constant over time. (17)

Patients most at risk for conventional NSAID-mediated ulcers and ulcer complications are the elderly, those with a history of GI ulcers or GI bleeding, and those with a history of cardiovascular disease. (18) Other potential risk factors include general debility, smoking, alcohol, NSAID intolerance, concurrent use of corticosteroids or anticoagulants, and possibly concomitant infection with *Helicobacter pylori*. (14,19,20)

Conventional NSAIDs may also cause small and large intestinal toxicity. NSAID enteropathy most often manifests as asymptomatic anemia but may include intestinal ulcers, perforations, or strictures. (21) The incidence of such events is difficult to determine as these toxic effects often go unrecognized.

In addition to pathologic effects on the GI tract mucosa, conventional NSAIDs also produce GI intolerance, which manifests as nonspecific symptoms such as dyspepsia, abdominal pain, and nausea. (3) Because such symptoms often occur in the absence of ulcers or ulcer complications, these symptoms are not necessarily predictive of serious GI toxicity. However, the occurrence of GI intolerance is a risk factor for more serious GI outcomes, indicating that GI tolerability and toxicity are interrelated. (14)

Another mechanism-based toxicity of conventional NSAIDs is platelet dysfunction. (22) Because platelet aggregation depends on COX-1-mediated production of thromboxane, conventional NSAIDs produce the potential for a bleeding diathesis by inhibiting COX-1 activity. (22) This effect is clinically evident in the context of surgery or accidental injury and may contribute to GI toxicity as well. This property of conventional NSAIDs also complicates the concomitant use of anticoagulant agents such as warfarin.

Renal dysfunction is also a side effect of chronic conventional NSAID therapy. This may manifest as either acute alterations in renal function (e.g., a decline in glomerular filtration or sodium retention leading to congestive heart failure, edema, or hypertension) or more chronic syndromes (e.g., interstitial nephritis or papillary necrosis). (23) The incidence of serious renal dysfunction is lower than that of GI toxicity; it has been estimated that the incidence of hospitalization for acute renal failure secondary to conventional NSAIDs is on the order of 15 to 20 per 100,000 patient-years. (24)

Finally, conventional NSAIDs are associated with a variety of adverse effects that are not mechanism-based but are more likely idiosyncratic or immunologic in nature. The more common of these effects are hepatotoxicity and cutaneous reactions (25,26), although occurrence of more serious forms such as hepatic failure or exfoliative dermatitis (e.g., Stevens-Johnson syndrome) is rare. (27)

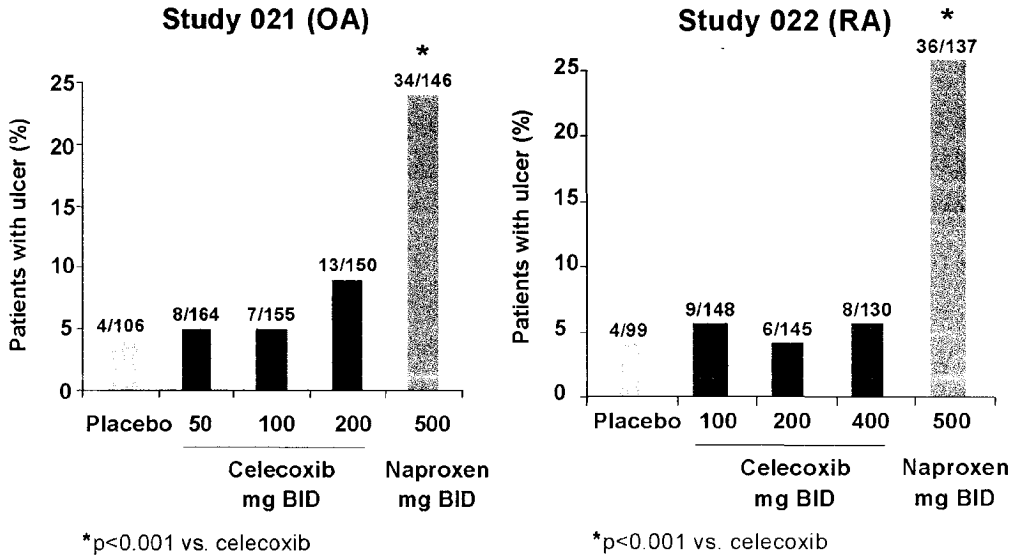
2.3. Celecoxib Safety Profile Derived from the Original NDA

The celecoxib NDA contained data from 51 completed clinical studies involving over 13,000 unique patients or healthy volunteers, of which over 9400 received celecoxib. These trials established that celecoxib is safe and effective in the treatment of OA (maximally effective and recommended daily dose of 200 mg) and adult RA (maximally effective and recommended daily dose of 200-400 mg), and is comparably effective to full therapeutic doses of conventional NSAIDs (naproxen, ibuprofen, and diclofenac). (9,10)

The GI safety profile of celecoxib was established in six endoscopy trials. (9) The results from the two pivotal OA and RA trials that included endoscopy are shown in Figure 2.b. These studies established that celecoxib up to 800 mg daily is associated with an incidence of gastroduodenal ulcers over 12 weeks that is similar to placebo and significantly less than that observed with typical therapeutic doses of naproxen. Similar results were

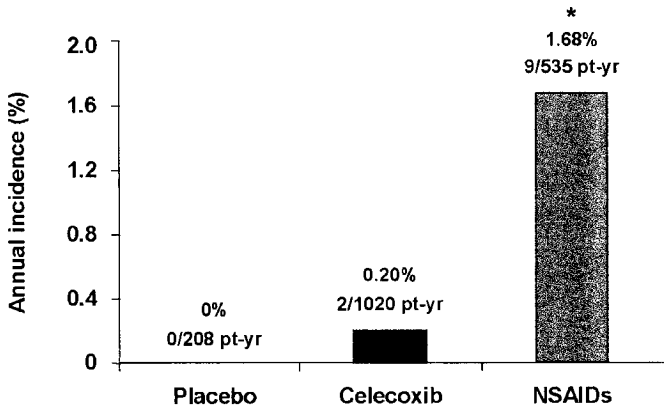
derived from serial endoscopic studies comparing celecoxib at 400 mg daily to standard therapeutic doses of naproxen, ibuprofen, and diclofenac, and from an additional endoscopic study comparing celecoxib with diclofenac that did not require a baseline endoscopy.

Figure 2.b. Gastroduodenal Ulcer Incidences over 12 Weeks in Pivotal OA and RA Trials: Original Celecoxib NDA



A prospective blinded review of all potential clinically significant upper GI events (ulcer complications consisting of bleeding, perforation, and gastric outlet obstruction) from the controlled arthritis trials by an independent GI Events Committee was also performed. As shown in Figure 2.c, the derived annualized rates were 0%, 0.20%, and 1.68% in patients receiving placebo, celecoxib, and conventional NSAIDs, respectively. (9)

Figure 2.c. Annual Incidence of Ulcer Complications in Controlled Clinical Trials: Original Celecoxib NDA



*p<0.05 vs. celecoxib

In terms of overall GI tolerability, celecoxib was well tolerated, with significantly higher incidences of dyspepsia, diarrhea, and flatulence than placebo (Table 2.a). Celecoxib was generally better tolerated than conventional NSAIDs, with significantly lower incidences of dyspepsia, abdominal pain, nausea, constipation, and flatulence.

Table 2.a. Analysis of GI Adverse Events between Celecoxib and Either Placebo or NSAIDs: Original Celecoxib NDA

Adverse Event	Celecoxib*	Placebo	p Value	Celecoxib*	NSAID	p Value
No. treated	3512	1864		2890	2098	
Any GI event	23.5	18.5	<0.001	27.7	35.4	<0.001
Dyspepsia	8.4	6.2	0.004	9.9	12.0	0.021
Diarrhea	5.4	3.8	0.008	6.2	6.1	-
Abdominal pain	3.5	2.8	-	4.9	8.2	<0.001
Nausea	3.6	4.2	-	3.8	5.6	0.002
Flatulence	2.1	1.0	0.003	2.2	3.7	0.003
Constipation	1.8	1.9	-	1.9	4.1	<0.001
Tooth disorder	1.7	1.5	-	1.9	2.2	-
Vomiting	0.9	0.5	-	1.3	1.6	-

Derived from Celecoxib Integrated Summary of Safety Information. (9) Data represent percentages of patients unless otherwise indicated.
*Includes celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.

Five previously reported clinical studies were undertaken to compare the effects of celecoxib on platelet function with those of conventional NSAIDs. (9) The results of two studies employing a dose of 1200 mg daily demonstrated that celecoxib at six times the maximally effective OA dose and three times the maximally effective RA dose did not

inhibit platelet aggregation or increase bleeding time. A subsequent study performed with celecoxib doses up to 2400 mg daily confirmed these results.

The incidence of renal adverse effects of celecoxib reported in the original NDA was low but discernibly greater than placebo. (9) The most common renal adverse event was peripheral edema. Overall, the incidence was similar to conventional NSAIDs, but no dose-related increase was observed. Celecoxib was not associated with measurable changes in glomerular filtration in subgroups that are considered susceptible to the renal effects of conventional NSAIDs (i.e., the elderly and those with renal insufficiency). However, transient reductions in urinary sodium excretion were evident with celecoxib that were comparable in degree to conventional NSAIDs. The data from the NDA thus did not establish a clear safety benefit between celecoxib and conventional NSAIDs with respect to renal effects.

The data from the NDA indicated that celecoxib is not associated with alterations in liver function or with adverse events due to liver disease. (9) Liver function test abnormalities were rare and seen only at rates similar to or less than placebo and significantly less than conventional NSAIDs.

Cutaneous reactions to celecoxib were observed at a rate not significantly greater than that observed in the placebo or conventional NSAID group. (9) A small but statistically significant increase in withdrawals due to rash was noted relative to comparator NSAIDs.

3. CLASS TRIAL: STUDY DESIGN AND PATIENT DISPOSITION

3.1. Study Objectives

The primary objective of the CLASS trial was to compare the incidence of ulcer complications (upper GI bleeding, perforation, and gastric outlet obstruction) associated with celecoxib 400 mg BID to that associated with ibuprofen 800 mg TID (protocol N49-98-02-035) or diclofenac 75 mg BID (protocol N49-98-02-102) in patients with OA or RA.

The secondary safety objectives of the study were the following:

- To compare the chronic overall safety and tolerability of celecoxib versus ibuprofen and diclofenac (hereafter collectively referred to as "NSAIDs").
- To evaluate potential risk factors (e.g., age, gender, *H. pylori* infection, type of arthritis, cardiovascular disease, concurrent use of oral corticosteroids, history of peptic ulcer and/or GI bleeding, alcohol, tobacco, and aspirin use) for their impact on the effect of treatment on outcome.

An evaluation of risk factors was specifically included to facilitate the evaluation of GI safety in the event that bias was introduced by such risk factors.

3.2. Investigational Plan and Endpoints

3.2.1. Study Design

Patients were randomly assigned to receive either celecoxib 400 mg BID or comparator NSAID (ibuprofen 800 mg TID in protocol N49-98-02-035 or diclofenac 75 mg BID in protocol N49-98-02-102) in a balanced randomization that was stratified by OA/RA status.

The dose of celecoxib evaluated in this study (400 mg BID) was two to four times the maximally effective doses for RA and OA, respectively, and was chosen to ensure that the ulcerogenic potential of the drug was rigorously assessed.

The ibuprofen dose of 800 mg TID and the diclofenac dose of 75 mg BID were chosen, since these represent the most commonly prescribed doses of the two drugs for treating OA and RA. (28)

Total combined enrollment was planned to reach approximately 4000 patients receiving celecoxib and 2000 patients receiving each NSAID comparator, for a total of 8000 patients. Patients underwent Screening/Baseline visits and follow-up visits scheduled for 4, 13, 26, 39, and 52 weeks (and 65 weeks in protocol N49-98-02-035 only) after the first dose of study medication.

3.2.2. Study Population

3.2.2.1. Inclusion Criteria

To qualify for study participation, candidates must have:

- Been of legal age of consent or older;
- For women of childbearing potential, been using adequate contraception since last menses and agreed to continue to use adequate contraception during the study, not been lactating, and had a negative serum pregnancy test within seven days before receiving the first dose of study medication;
- Had a documented clinical diagnosis of OA or RA of at least three months duration; and
- Required chronic NSAID therapy in the Investigator's opinion.

3.2.2.2. Exclusion Criteria

Candidates were excluded from participation if they satisfied any of the following criteria:

- Had an active malignancy of any type or history of malignancy (except basal cell carcinoma that had been treated, or a history of other malignancies that had been surgically removed without recurrence for at least five years);
- Had been diagnosed as having or had received treatment for esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days prior to receiving the first dose of study medication;
- Had active GI disease (e.g., inflammatory bowel disease);
- Had a history of gastric or duodenal surgery other than simple oversew of an ulcer or perforation;
- Had significant renal or hepatic dysfunction, or a significant coagulation defect considered by the Investigator to be clinically significant;
- Had abnormal Screening laboratory test values >1.5 times the upper limit of normal (ULN) for either aspartate aminotransferase (AST [SGOT]) or alanine

aminotransferase (ALT [SGPT]) or any other laboratory abnormality at Screening considered by the Investigator to be clinically significant;

- Had a positive screening fecal occult blood test result;
- Had a known hypersensitivity to COX-2 inhibitors, sulfonamides, ibuprofen (protocol N49-98-02-035) or diclofenac (protocol N49-98-02-102);
- Had received any investigational medication within 30 days before the first dose of study medication or was scheduled to receive an investigational drug other than celecoxib during the course of the study;
- Had previously been admitted to either of these protocols or a prior study with celecoxib.

At each visit after the Baseline Visit, patients answered the following question: "Since your last visit, have you experienced or do you currently have any symptoms that are not associated with your arthritis?" If any sign or symptom was suggestive, in the Investigator's opinion, of an ulcer complication (i.e., upper GI bleeding, perforation, or gastric outlet obstruction), the Investigator was to initiate a work-up of the potential event according to the algorithm shown in Table 3.a. Potentially suggestive signs or symptoms included, but were not limited to, abdominal pain, protracted nausea and vomiting, hematemesis, melena, and decreased hemoglobin or hematocrit. Study personnel were instructed that clinical judgment and the administration of standard medical care should take precedence over the algorithm in the evaluation and treatment of any patient in the study.

Table 3.a. Algorithm for Work-up of Suspected Ulcer Complications

Presentation	Initial Evaluation	Work-up
Clinical situations requiring emergent or urgent attention **For all patients with the following presentations:** • **Obtain base data (hematocrit, stool heme x3, and postural vital signs) as part of initial evaluation.** • **Test for *H. pylori* infection as part of work-up (Meretek UBT, CLOtest or H&E).** • **Notify Searle medical monitor and Safety Specialist immediately. Provide contact information.** • **Complete GI event CRFs.**		
Severe acute abdominal pain/acute abdomen	EMERGENT: • Evaluation for perforating ulcer including base data	• Documentation of perforation by surgery or by laparoscopy with radiographic evidence of free air in abdomen • Test for *H. pylori* infection
Intractable abdominal pain with nausea/vomiting	EMERGENT: • Evaluation for gastric outlet obstruction including base data	• Documentation of gastric outlet obstruction with UGI study (radiographic or endoscopic) • Test for *H. pylori* infection
Hematemesis or melena	EMERGENT: • Evaluation for GI bleeding source including base data	• Documentation of bleeding source by UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain
Acute hypovolemia/hypotension	EMERGENT: • Evaluation for acute GI blood loss including base data	• If GI evaluation positive (e.g., blood in nasogastric aspirate, heme positive stool, or hematocrit decreased by 5% or more [absolute change]), investigate source with UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain
Current/recent (<14 days) history of: • melena (black tarry stool) or • black stool which is a change in normal pattern	IMMEDIATE: • Obtain base data	• If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain • If work-up negative, retest stool for heme and repeat hematocrit in 1-2 weeks
Development of: • postural dizziness or lightheadedness • syncope	IMMEDIATE: • Obtain base data • If patient orthostatic, evaluate for acute GI blood loss	• If GI evaluation positive (e.g., blood in nasogastric aspirate, heme positive stool, or hematocrit decreased by 5% or more [absolute change]), investigate source with UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain
Clinical situations requiring prompt attention **For all patients with the following presentations:** • **Obtain base data (hematocrit, stool heme x3, and postural vital signs) as soon as possible.** • **Test for *H. pylori* infection as part of work up (Meretek UBT, CLOtest or H&E)** • **Notify Safety Specialist as soon as possible.** • **Complete GI event CRFs.**		
History of dark stool: • >14 days previously, or • vaguely characterized, or • with concurrent iron/bismuth ingestion	ASAP: • Obtain base data	• If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain
History of : • hematochezia, or • anal/rectal bleeding after elimination	ASAP: • Obtain base data	• Perform colonoscopy • UGI endoscopy at Investigator's discretion (test for *H. pylori* infection)
Development of:	ASAP:	• If stools heme positive or studies indicate

Presentation	Initial Evaluation	Work-up
• New anemia, or • Drop in hematocrit of 5% or more (absolute change)	• Obtain base data including ferritin, iron, iron binding capacity, MCV, MCHC	iron deficiency, perform UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain
Development of: • Dyspepsia, or • Abdominal pain, or • Nausea/vomiting	ASAP: • Obtain base data	• If any component of work-up positive (stool heme positive, hematocrit decreased by 5% or more [absolute change], or patient orthostatic), perform UGI endoscopy (test for *H. pylori* infection) • Additional studies as indicated by "ordinary care"
Development of: • Heme-positive stools	ASAP: • Obtain base data	• Perform UGI endoscopy (test for *H. pylori* infection) • Lower GI work-up if bleeding source uncertain

CRF represents case report form; H&E, hematoxylin-eosin; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration.

3.2.3. Adjudication Process for Potential Ulcer Complications

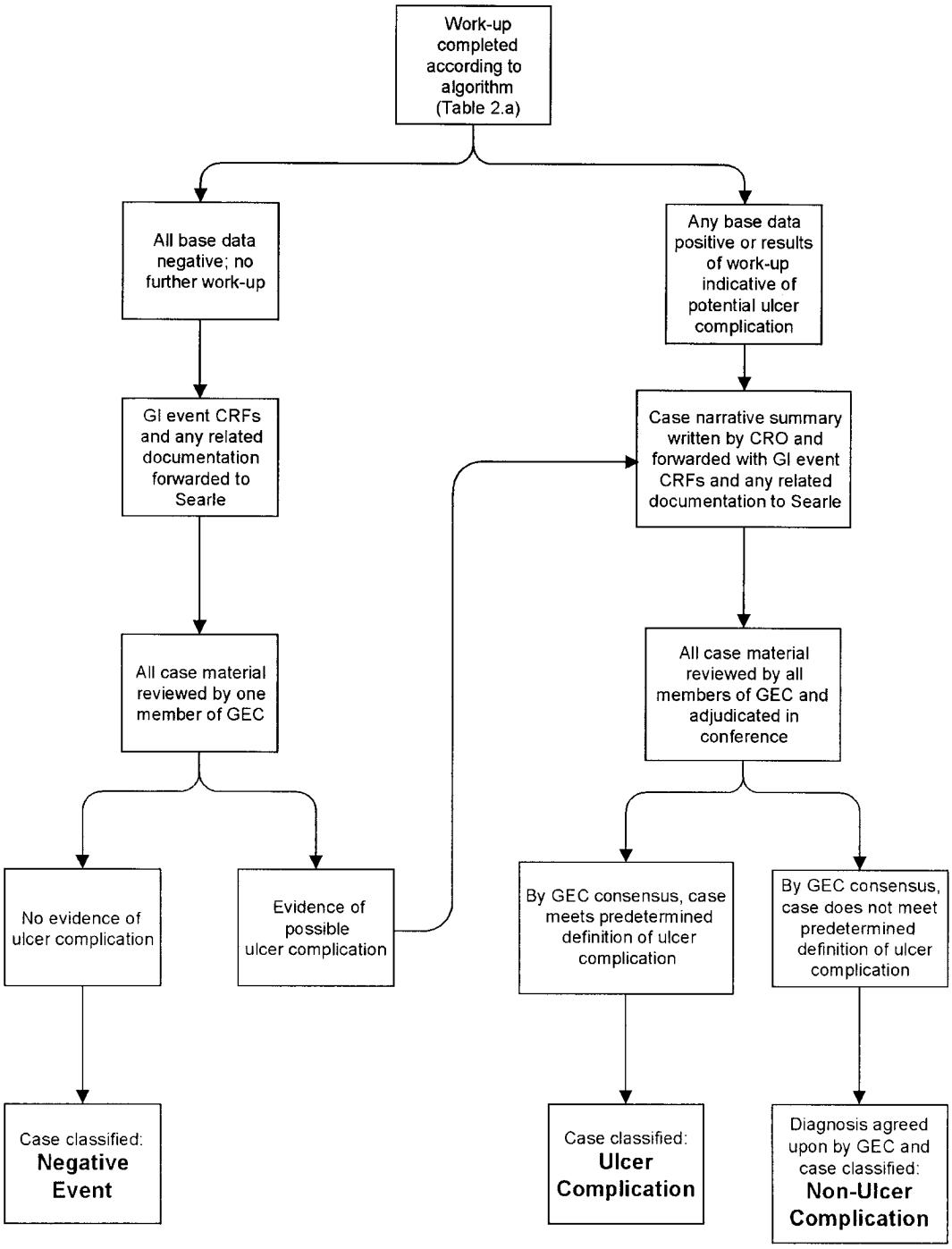
Potential ulcer complications were reviewed and adjudicated as outlined in Figure 3.a by an independent Gastrointestinal Events Committee (GEC) consisting of four expert gastroenterologists. The GEC members were Jay L. Goldstein, MD (chair), Naurang M. Agrawal, MD, William Stenson, MD, and Glenn Eisen, MD. In all of their activities related to reviewing and adjudicating potential ulcer complications, all GEC members were blinded to all patients' study and treatment assignments.

In brief, all data on potential ulcer complications, including the GI event CRFs and any source documentation (e.g., laboratory reports, endoscopy reports and photographs, radiology reports, and hospital discharge summaries) were forwarded to Searle from the site. If none of the base data suggested an ulcer complication, then the case was reviewed in a blinded fashion by a single member of the GEC (these cases were assigned to GEC members alphabetically by the patient's initials). The GEC member either confirmed that there was no evidence of an ulcer complication and the case was classified as a negative event, or chose to send the case material to the full GEC for adjudication.

If any base data or work-up results were suggestive of a ulcer complication, a narrative summary of the case was written. This summary and other relevant documentation were then reviewed by all members of the GEC. The decision whether the case met the definition of an ulcer complication was reached by unanimous consensus. Those events that were adjudicated and considered by unanimous consensus not to meet the predetermined criteria are referred to as non-ulcer complications.

At any point during the review and adjudication process, the Investigator may have been contacted to request further information or follow-up.

Figure 3.a. Data Flow and Adjudication of Potential Ulcer Complications



3.2.3.1. Pre-specified Definitions of An Ulcer Complication

The definitions listed below were based on those used in the MUCOSA trial (18) and in the celecoxib NDA.

3.2.3.1.1. UGI Bleeding (Category 1)

Upper GI bleeding was categorized as one of the following seven clinical presentations:

- Hematemesis with a gastric or duodenal ulcer or large erosion proven by endoscopy or an upper GI barium x-ray (category 1A).
- A gastric or duodenal ulcer or large erosion proven by endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or attached clot to base of an ulcer; category 1B).
- Melena with a gastric or duodenal ulcer or large erosion proven by endoscopy or barium upper GI x-ray (category 1C).
- Hemoccult-positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or barium upper GI x-ray and with bleeding as evidenced by a fall in hematocrit ≥5 percentage points or a reduction of hemoglobin >1.5 g/dL from Baseline (category 1D-1).
- Hemoccult-positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or barium upper GI x-ray and with bleeding as evidenced by orthostasis (changes to postural vital signs: increase in pulse rate of ≥20 beats/min and/or a decrease in systolic blood pressure of ≥20 mm Hg and/or diastolic blood pressure of ≥10 mm Hg; category 1D-2).
- Hemoccult-positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or barium upper GI x-ray and with bleeding as evidenced by a need for blood transfusion of two or more units (category 1D-3).
- Hemoccult-positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or barium upper GI x-ray and with bleeding as evidenced by blood in the stomach as determined by endoscopy or nasogastric aspiration (category 1D-4).

3.2.3.1.2. UGI Perforation (Category 2)

Upper GI perforation was defined as an opening in the wall of the stomach or duodenum requiring surgery or laparoscopic repair, but only if the evidence was unequivocal (free air, peritoneal irritation signs, etc.).

3.2.3.1.3. Gastric Outlet Obstruction (Category 3)

Occurrence of a gastric outlet obstruction was based on the opinion of the clinician with endoscopic or upper GI barium x-ray documentation. Endoscopic evidence included a tight edematous pylorus with an ulcer in the pyloric channel, inability to pass the endoscope tip into the duodenal bulb or descending duodenum, or retained fluid/food in the stomach. Upper GI barium x-ray evidence of obstruction included:

- A dilated stomach.
- A slowly emptying stomach in a patient with clinical evidence of outlet obstruction and in some instances with an ulcer in the channel or duodenal bulb.
- Severe narrowing and edema obstructing the outlet of the stomach.

3.2.3.2. Categorization of Patient Participation

Patients who took study medication for the full scheduled Treatment Period or were continuing to take study medication when the trial officially concluded were considered to have completed the study. Patients terminating study participation before completing the full Treatment Period and before the trial officially concluded were considered to have withdrawn. Reasons for withdrawal were classified as follows:

- Lost to follow-up
- Pre-existing violation of entry criteria
- Protocol noncompliance (failure to comply with the requirements of the protocol, e.g., failure to take at least 70% of the study medication in any 13-week dispensing interval)
- Treatment failure (arthritis signs and symptoms were not controlled)
- Adverse sign or symptom (including an ulcer found detected by endoscopy)

Patients found to have a gastric or duodenal ulcer were required to be withdrawn from the study and treated according to the clinical judgment of the Investigator.

Patients terminating early from the study were contacted by telephone monthly for two months or until the official conclusion of the study, whichever occurred first, to gather pharmacoeconomic information as well as to determine if an ulcer complication had occurred. Reasonable attempts were made to contact each patient.

3.2.3.3. Prior and Concomitant Therapy

No medications were prohibited prior to entering the study except the use of any investigational drug within 30 days prior to receiving the first dose of study medication. No NSAID washout period was performed.

Patients were instructed to avoid the use of any medication other than the drugs provided, if at all possible, during the Treatment Period. The following drugs were specifically excluded:

- NSAIDs, either prescription or nonprescription. Patients taking ≤325 mg aspirin per day for reasons other than arthritis, for at least 30 days before the first dose of study medication, were allowed to continue the same dose regimen for the duration of the study.
- Anti-ulcer drugs (including H_2 antagonists, proton pump inhibitors, sucralfate, and misoprostol), either prescription or nonprescription. Short-term use of antacids (up to seven days of more than one dose per day each month) and daily use of calcium-containing antacids as a calcium supplement (e.g., for osteoporosis) was permitted.
- Antibiotics (i.e., amoxicillin, clarithromycin, azithromycin, tetracycline, metronidazole, or bismuth) used alone or combined with omeprazole, lansoprazole, or ranitidine specifically as treatment for *H. pylori* infection.
- Antineoplastics (other than methotrexate ≤25 mg per week or azathioprine as treatment for RA).

Acetaminophen (≤2 g per day, alone or in combination with propoxyphene hydrochloride or napsylate, hydromorphone hydrochloride, oxycodone hydrochloride, or codeine phosphate) was permitted as necessary throughout the study. Oral, intramuscular, and intra-articular corticosteroids were also allowed.

3.2.4. Statistical Methods Planned in the Protocol

The two trials described in this Briefing Document were prospectively designed with the intent to combine the data into a pooled analysis. Therefore, the statistical analyses described in this section were performed on a single, combined data set in which celecoxib patients from both protocols were pooled into a single treatment group for comparison with patients in the diclofenac 75 mg BID and ibuprofen 800 mg TID treatment groups. To verify homogeneity between the celecoxib groups in the two protocols, all of the summaries and analyses of patient disposition, reasons for termination, and Baseline variables were repeated with the two celecoxib treatment groups from the two protocols separately analyzed.

The statistical analysis plan for the upper GI safety results in this study was developed in discussion with FDA representatives, and the approved version of the plan was submitted to the FDA prior to study closure.

3.2.4.1. Analyses of Baseline Data

Analyses of Baseline data were performed on the Intent-to-Treat Cohort, defined as all randomized patients who received at least one dose of study medication.

3.2.4.2. GI Safety Analyses

All analyses of GI safety were carried out on the Intent-to-Treat Cohort.

For the two GI safety endpoints of primary interest, namely (i) ulcer complications and (ii) ulcer complications combined with symptomatic ulcers, the analyses were performed for the following categories of patients in the first six months of treatment: all patients, patients not taking aspirin, and patients taking aspirin. These analyses were based on the assessment of risk factors prespecified in the protocol (see Section 4.3).

As stated above, the primary endpoint in the GI safety analyses was the development of an ulcer complication (i.e., upper GI bleeding, perforation, or obstruction). The null hypothesis being tested was that there is no difference between the incidence of ulcer complications associated with celecoxib and that associated with either of the NSAID groups. Because the development of an ulcer is a necessary precursor to the development

of an ulcer complication, all analyses of ulcer complications in this study were repeated for patients who experienced either an ulcer complication or symptomatic ulcer.

In the primary analyses of ulcer complications and ulcer complications/symptomatic ulcers, events not considered to be possibly related to study drug were censored as follows. Events occurring before 48 hours after midnight of the first dose day were censored and not included in the analysis. Similarly, any event occurring more than 48 hours after midnight of the last dose day was censored from the analysis, unless it occurred within two weeks after the last dose of study medication and the GEC determined that it was treatment-related (i.e., it was unlikely to be related to any intervening confounding factors). In these analyses, onset of an ulcer complication was defined as the day on which signs or symptoms first occurred that were suggestive of a potential ulcer complication; onset of an ulcer was defined as the day of the endoscopy that disclosed the ulcer.

In the analyses of both ulcer complications and ulcer complications/symptomatic ulcers, the log-rank test was used to compare the time-to-event curves between celecoxib 400 mg BID and the two NSAIDs combined, as well as between celecoxib 400 mg BID and each of the NSAIDs separately as a stepwise procedure. Each test was performed at the alpha level of 0.05 (two-sided). In these analyses, patients completing the study without the event of interest were censored at the Final Visit, and patients who withdrew from the study for reasons other than occurrence of an event were censored at the time of withdrawal. Because patients receiving celecoxib 400 mg BID from both protocols were pooled into a single group, the celecoxib results from the two protocols were also compared (numerically) to ensure homogeneity.

Potential risk factors for the development of an ulcer complication were identified prior to analysis. These included demographic and disease characteristics (age, gender, disease type and duration, and Baseline disease severity), GI history (positive *H. pylori* serology, or history of upper GI bleeding, gastroduodenal ulcer, or NSAID intolerance), concomitant medication use (including aspirin use), alcohol use, and tobacco use. For each of these factors, factor effect and treatment-by-factor interaction, as well as within-group effects, were assessed based on time to event with a COX proportional hazards

model. All of these risk factor analyses were performed with the NSAID groups examined separately as well as with pooling of the two NSAID groups.

Additional multivariate analyses of risk factors were performed, as was modeling of the results to adjust for study-emergent imbalances between groups at risk for developing an ulcer or ulcer complication.

3.2.4.3. General Safety Analyses

All patients who took at least one dose of study medication were included in all safety analyses.

The incidences of treatment-emergent adverse events were tabulated by treatment group and body system, and pairwise compared between treatment groups using Fisher's Exact test. Events occurring more than 28 days after the last dose of study medication were excluded from all analyses.

Adverse events causing withdrawal were similarly analyzed. Serious adverse events were tabulated by treatment group and body system, but no statistical analysis was performed.

Contingency tables were prepared showing numbers of patients whose posttreatment laboratory results met certain criteria for combinations of values or changes in values that might indicate hematologic, hepatobiliary, or renal effects. These criteria represented decreases in both hemoglobin and hematocrit, increases in both creatinine and BUN, and increases in both AST and ALT. These tables showed the numbers of patients whose laboratory values shifted among various categories of increases and decreases according to predetermined cutoff values.

3.3. Patient Dispositon

A total of 8059 patients were randomized at 386 centers in the two protocols. Ninety-one patients were determined never to have taken any study medication. In the majority of these cases, the patients were assigned a randomization number and treatment before completing the screening procedures. These patients were never entered into the study or dispensed study medication. All subsequent tables and figures in this document, including all subgroup analyses, include or represent subsets of the Intent-to-Treat Cohort, which

included only those patients who took at least one dose of study medication. As noted above, the GI safety data are based on the six-month treatment timepoint according to the risk factor adjustment prespecified in the protocol.

3.3.1. Reasons for Termination

The reasons for termination from the study within the first six months are summarized in Table 3.b. A total of 4573 patients completed six months (182 days or more): 2376 (59.6%) receiving celecoxib 400 mg BID, 1148 (57.5%) receiving diclofenac 75 mg BID, and 1049 (52.8%) receiving ibuprofen 800 mg TID. The significant majority of withdrawals in all treatment groups were due to protocol noncompliance, treatment failure, or an adverse event. No patient was lost to follow-up.

Table 3.b. Reasons for Withdrawal: First Six Months

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Completed	59.6	57.5	52.8
Withdrawn	40.4	42.5	47.2
Lost to follow-up	0.0	0.0	0.0
Pre-existing violation	0.6	0.5	0.6
Protocol noncompliance	8.8	7.1	10.6
Treatment failure	12.6	12.7	16.9
Adverse event	18.4	22.2	19.1

Data represent percentages of patients.

Table 3.c displays the duration of exposure to treatment for all patients and patients not taking aspirin. The proportions of patients with between three and six months of exposure to treatment ranged from 64% to 70%.

Table 3.c. Duration of Exposure: First Six Months

Treatment Duration	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
All Patients			
3.1 to 6 months (%)	70	69	64
Total patient-years	1441.07	710.29	673.52
Patients not taking aspirin			
3.1 to 6 months (%)	70	69	64
Total patient-years	1143.05	559.21	541.48

3.3.2. Demographics and Other Baseline Characteristics

Baseline characteristics of all patients in the study are summarized in Table 3.d. While the three treatment groups were generally similar with respect to most Baseline parameters, statistically significant differences in age and distribution by race were observed.

Table 3.d. Demographic and Other Baseline Characteristics: All Patients

Characteristic	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Age*,			
mean (range), y	60.6 (20-89)	60.1 (21-90)	59.5 (18-90)
>65 (%)	39.1	38.2	36.4
>75 (%)	12.2	11.8	10.9
Women (%)	68.5	67.4	70.8
Race/ethnicity* (%)			
White	88.5	89.4	86.3
Black	7.5	7.6	8.7
Other	4.0	3.1	5.1
Primary RA (%)	27.3	27.2	27.8
Duration of disease, mean, y			
OA	10.3	10.4	10.0
RA	11.3	10.5	10.9
NSAID therapy (%)	81.4	81.0	81.3
Risk factor (%)			
History of GI bleeding	1.7	1.5	1.4
History of GI ulcer	8.4	8.5	7.6
Positive *H. pylori* serology	38.5	37.7	38.7
Cardiovascular disease	40.2	40.3	40.0
Concurrent medication (%)			
ASA (≤325 mg daily)	20.9	21.5	19.3
Corticosteroids	30.6	28.5	30.6

*Statistically significantly different among treatment groups at $p<0.05$ (p value from two-way analysis of variance with treatment group and center as factors).

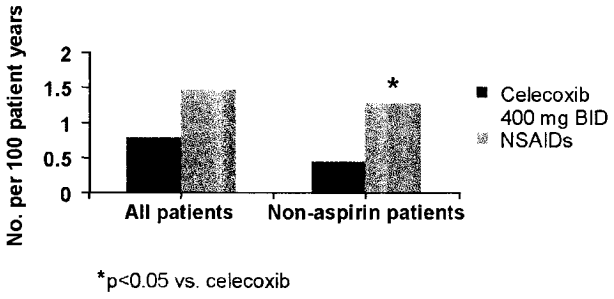
All Baseline and concurrent medication data were separately examined by protocol. This analysis demonstrated that the populations in the two protocols were essentially homogeneous with respect to demographic and other Baseline characteristics.

4. CLASS TRIAL: GI SAFETY BENEFITS

4.1. Ulcer complications

The ulcer complication data in the entire cohort over six months based on the uncensored patients are shown in Figure 4.a (expressed as events per 100 patient-years of exposure to study medication). The statistical comparisons are derived from log-rank tests of the time-to-event curves that are shown in Figures 4.b and 4.c.

Figure 4.a. **Annualized Incidences of Ulcer Complications**



*p<0.05 vs. celecoxib

Figure 4.b. **Kaplan-Meier Plot of Time to Ulcer Complication: All Patients**

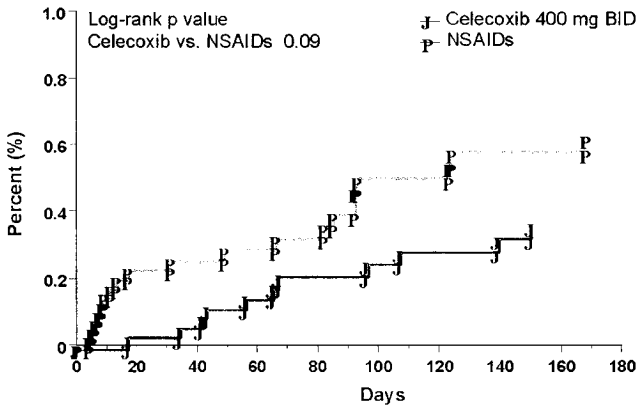
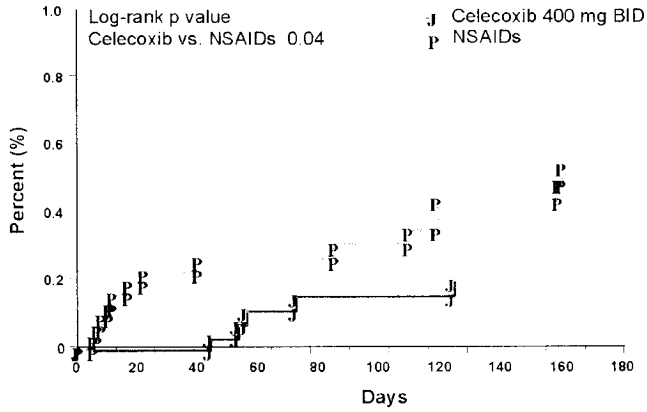


Figure 4.c. **Kaplan-Meier Plot of Time to Ulcer Complication: Patients not Taking Aspirin**



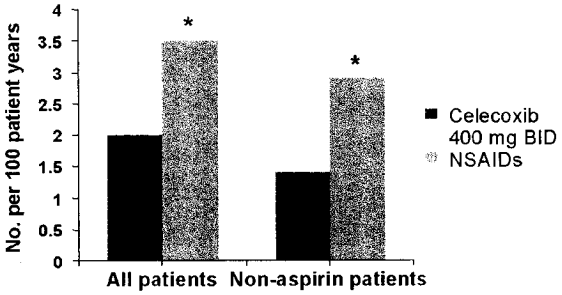
These data showed a numerical trend toward a decrease in the incidence of ulcer complications on celecoxib compared to NSAIDs combined. The lack of statistical significance was largely a function of the higher than expected observed event rate in the celecoxib group relative to the rate for celecoxib in the controlled clinical trials reported in the original NDA (0.76% vs. 0.20%). (12) The observed NSAID rate (1.45%), in contrast, was comparable to that seen in the original celecoxib trials (1.68%), as well as in the previously published MUCOSA trial and the ARAMIS database (1.96% and 1.58%, respectively). (14,18)

Analyses of risk factors for celecoxib and NSAIDs showed that aspirin was a significant risk factor for ulcer complications for patients on celecoxib (RR=4.5, p=0.01) but not for NSAIDs (RR=1.7, p=0.29). Therefore, an analysis of the non-aspirin using cohort was performed. In the non-aspirin using cohort, there was a statistically significant decrease in the incidence of ulcer complications observed with celecoxib relative to pooled NSAIDs (0.44% vs. 1.27%; Figures 3.a and 3.c). The annualized incidence rate for celecoxib of 0.44% (95% CI, 0.14%-1.0%) was comparable to the rate of 0.2% previously reported for celecoxib, and close to the background rate of ulcer complications in non-conventional NSAID users, which has been estimated to be approximately 0.1% to 0.4% on an annualized basis (varying as a function of patient age). (14,29) The small, apparent difference in risk between the observed rate of 0.44% and the background rate may be due to the use of over-the-counter conventional NSAIDs and non-acetylated salicylates. Such use was prevalent in the study and could have contributed to at least one of the ulcer complications in the celecoxib group.

4.2. Symptomatic Ulcers and Ulcer Complications

The ulcer complication/symptomatic ulcer data in the entire cohort at six months based on the uncensored patients are shown in Figure 4.d (expressed as events per 100 patient-years of exposure to study medication). The statistical comparisons are derived from log-rank tests of the time-to-event curves, which are shown in Figures 4.e and 4.f.

Figure 4.d. **Annualized Incidences of Ulcer Complications/Symptomatic Ulcers**



*p<0.05 vs. celecoxib

Figure 4.e. **Kaplan-Meier Plot of Time to Ulcer Complication/ Symptomatic Ulcer: All Patients**

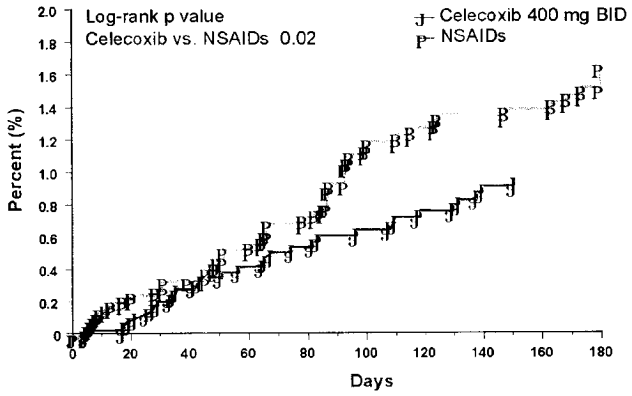
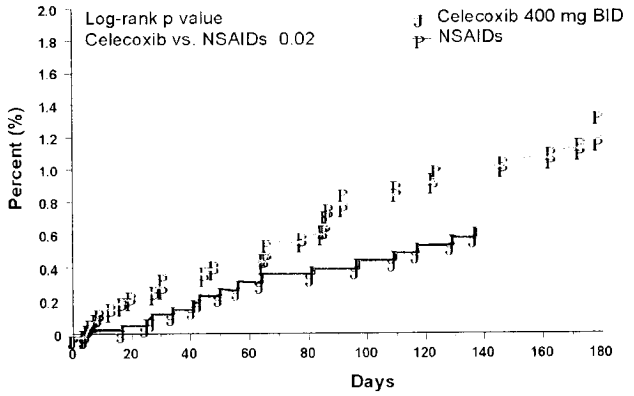


Figure 4.f. **Kaplan-Meier Plot of Time to Ulcer Complication/Symptomatic Ulcer: Patients not Taking Aspirin**



The incidence of ulcer complications/symptomatic ulcers was significantly lower in the celecoxib treatment group versus the NSAID treatment group: 2.08% and 3.54% for celecoxib and NSAIDs, respectively. This analysis also showed a significant difference in the incidences of ulcer complications/symptomatic ulcers in patients not receiving aspirin: 1.40% and 2.91%, respectively, for celecoxib and NSAIDs (Figures 4.d and 4.f).

4.3. Risk Factor Analysis and Basis of Six-Month Analyses

Univariate risk factor analysis (Table 4.a) indicated that there were five common risk factors for ulcer complications/symptomatic ulcers for celecoxib and NSAIDS: age ≥75 years, history of upper GI bleeding, history of gastroduodenal ulcer, cardiovascular disease, and aspirin use. The first four risk factors were the same conventional NSAID risk factors identified in the MUCOSA study. (18) Multivariate regression established that aspirin use was the most important risk factor for celecoxib and the least important risk factor for NSAIDS. The association of NSAID risk factors with celecoxib may in part result from concomitant aspirin use.

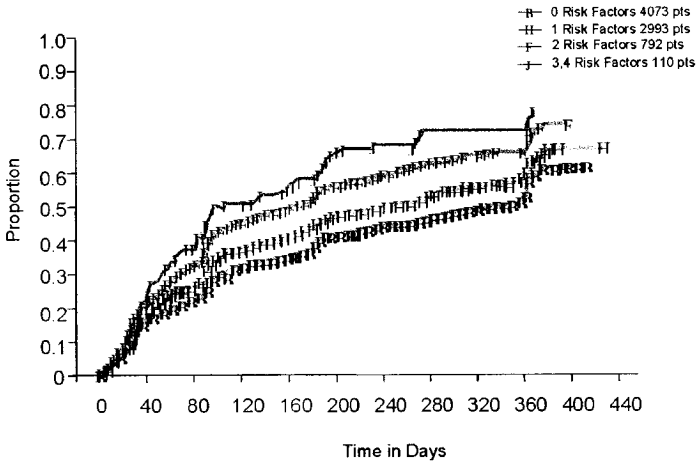
Table 4.a. Univariate Analysis of Risk Factors for Ulcer Complications and Ulcer Complications/Symptomatic Ulcers

Factor	Relative Risk			
	Ulcer Complications		Ulcer Complications/ Symptomatic Ulcers	
	Celecoxib 400 mg BID	NSAIDs	Celecoxib 400 mg BID	NSAIDs
Age ≥75 years	5.0 (p<0.001)	5.8 (p<0.001)	3.5 (p<0.001)	3.7 (p<0.001)
Patient's Global Assessment (Baseline)	2.5 (p=0.037)	2.4 (p=0.045)	1.4 (p=0.202)	1.4 (p=0.144)
History of UGI bleeding	3.6 (p=0.144)	7.1 (p=0.006)	4.3 (p=0.006)	3.4 (p=0.019)
History of GD ulcer	1.5 (p=0.509)	3.6 (p=0.009)	2.9 (p=0.002)	2.7 (p<0.001)
History of NSAID intolerance	2.2 (p=0.183)	2.3 (p=0.105)	3.2 (p=0.001)	1.9 (p=0.037)
History of CV disease	6.9 (p=0.002)	1.6 (p=0.240)	2.5 (p=0.002)	1.6 (p=0.048)
Positive *H. pylori* serology	0.7 (p=0.460)	2.2 (p=0.072)	1.1 (p=0.423)	2.0 (p=0.005)
Aspirin use	4.0 (p=0.005)	1.8 (p=0.211)	3.7 (p<0.001)	2.3 (p=0.002)

A marked withdrawal of patients with the aforementioned NSAID risk factors (i.e., age ≥75 years, history of GI bleeding, history of GI ulcer, or history of CV disease) occurred during the initial six months of the study (Figure 4.g). Withdrawal rates were higher in proportion to the number of risk factors, thus differentially removing the patients most likely to develop endpoint events in the NSAID groups from the trial during this interval (i.e., depletion of susceptible patients). This depletion of susceptible patients was

reflected in a virtual cessation of ulcer complications in the study after six months. Therefore, the six-month analysis represents a less biased assessment of the event rates for the treatment groups, more applicable to clinical practice in that high-risk patients who no longer take a particular conventional NSAID would subsequently be exposed to other conventional NSAIDs.

Figure 4.g. **Kaplan-Meier Plot of Time to Withdrawal by Number of Risk Factors: Age >75 Years and History of GI Bleeding, Ulcer, or Cardiovascular Disease**



4.4. Comparisons of Event Rates Between Celecoxib and Individual NSAID Comparators

The individual comparisons with ibuprofen and diclofenac for ulcer complications and ulcer complications/symptomatic ulcers are shown in Table 4.b. All comparisons significant for celecoxib versus NSAIDs combined were also significant for celecoxib versus ibuprofen. Numerical trends were noted between celecoxib and diclofenac cohorts for both of the endpoints. The absence of significant differences between these two groups, however, was likely a function of the high withdrawal rate for GI adverse events in patients receiving diclofenac (i.e., informative censoring) as follows.

Table 4.b. Incidences of Ulcer Complications/Symptomatic Ulcers for Individual Treatment Groups

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank p Values for Celecoxib vs.		
				Diclo	Ibu	Both
All Patients						
Ulcer Complications	0.76	1.27	1.63	0.264	0.073	0.092
Ulcer Complications/ Symptomatic Ulcers	2.08	2.82	4.31	0.308	0.005	0.023
Patients not Taking Aspirin						
Ulcer Complications	0.44	0.72	1.85	0.476	0.005	0.037
Ulcer Complications/ Symptomatic Ulcers	1.40	1.61	4.25	0.760	<0.001	0.017

4.5. Informative Censoring

A fundamental assumption of a survival analysis is that subjects will not alter drug intake or withdraw from a study due to signs or symptoms that precede the study endpoint. (20) In statistical terms, the log-rank test statistic assumes that censoring is independent of a likelihood of an outcome event. Published data suggest that this assumption may not hold true in trials of conventional NSAID-associated risks (or in statistical terms, that informative censoring may alter conventional NSAID-associated event rates). (20) This assumption appears to have been violated in this trial, particularly within the diclofenac treatment arm.

Treatment-emergent GI symptoms (moderate-to-severe abdominal pain, diarrhea, dyspepsia, nausea, and vomiting) were identified as a risk factor in this study for both ulcer complications and ulcer complications/symptomatic ulcers, most notably so for diclofenac. The relative risk of an ulcer complication in patients with moderate-to-severe GI symptoms versus patients without moderate-to-severe GI symptoms was 3.9 overall and 13.8 for diclofenac individually. The relative risk of an ulcer complication/ symptomatic ulcer in patients with moderate-to-severe GI symptoms versus patients without moderate-to-severe GI symptoms was 6.3 overall and 11.5 for diclofenac individually.

Withdrawals due to moderate-to-severe GI symptoms were also higher in the diclofenac group versus the other treatment arms (9.5% for diclofenac vs.7.5% for celecoxib and ibuprofen, $p<0.05$ for diclofenac vs. celecoxib). This significantly higher withdrawal rate

due to moderate-to-severe GI symptoms for the diclofenac group thus led to the early withdrawal of patients at risk of an endpoint event within this treatment arm, biasing the observed event rates associated with diclofenac (i.e., informative censoring). Therefore, standard analysis and interpretation of the event rate associated in this study with diclofenac may be misleading.

To adjust for this source of bias, an imputation of lost endpoint events was performed using the observed event rate in patients with GI symptoms who remained in the study and the calculated lost exposure due to dropouts for GI symptoms. (30-32) This analysis is shown in Table 4.c.

Table 4.c. Numbers and Crude Incidence Rates of Ulcer Complications and Ulcer Complications/Symptomatic Ulcers Adjusted for Withdrawals for GI Adverse Events: Six-Month Study Period

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	p Value	
				Celecoxib vs. Diclofenac	Celecoxib vs. Ibuprofen
Observed Rates					
Ulcer Complications	11 (0.3%)	9 (0.5%)	11 (0.6%)	0.264	0.073
Ulcer Complications + Symptomatic Ulcers	30 (0.8%)	20 (1.0%)	29 (1.5%)	0.308	0.005
Adjusted Rates					
Ulcer Complications	15 (0.4%)	16 (0.8%)	16 (0.8%)	0.036	0.035
Ulcer Complications + Symptomatic Ulcers	44 (1.1%)	34 (1.7%)	44 (2.2%)	0.069	0.001

The adjusted event rates for diclofenac approach those for ibuprofen, and differences between diclofenac and celecoxib become apparent.

4.6. GI Safety Conclusions

Based on these findings, it is thus concluded that:

- Celecoxib at 400 mg BID is associated with a lower rate of ulcer complications relative to conventional NSAIDs (and ibuprofen specifically).
- Celecoxib is associated with a lower rate of ulcer complications/symptomatic ulcers relative to conventional NSAIDs (and ibuprofen specifically).
- Aspirin use is an independent cause of ulcers in patients receiving celecoxib and mitigates the benefit of celecoxib in terms of risk reduction.
- Celecoxib cannot be meaningfully compared to diclofenac with respect to ulcer complications or ulcer complications/symptomatic ulcers using standard survival analysis because diclofenac is associated with a higher withdrawal rate due to GI adverse events, which represent precursors to clinically significant events.

5. CLASS TRIAL: GENERAL SAFETY

5.1. Adverse Events

Overall, the adverse event profile of celecoxib in this trial was similar to that reported in the original NDA. The most common adverse events that occurred in the CLASS trial are summarized in Table 5.a. Celecoxib was generally better tolerated than diclofenac or ibuprofen.

Table 5.a. Adverse Events with Incidence ≥3% in Any Treatment Group: Entire Study Period

Adverse Event	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
Any event	81.8	82.9	79.5*
Dyspepsia	16.5	19.5*	16.5
URTI	15.4	14.7	15.8
Headache	13.9	16.6*	13.0
Abdominal pain	11.7	18.5*	11.3
Diarrhea	10.9	15.0*	7.5*
Sinusitis	8.8	8.6	9.5
Nausea	8.2	12.1*	9.0
Flatulence	7.3	11.4*	7.2
Rash	6.2	2.8*	3.8*
Influenza-like symptoms	5.4	5.6	6.1
Injury accidental	5.3	5.0	5.5
Anemia	4.4	5.3	8.7*
Coughing	4.4	3.5	4.6
Rhinitis	4.3	3.9	3.7
Bronchitis	4.0	4.1	5.1*
Back pain	3.7	3.3	4.0
Edema peripheral	3.7	3.5	5.2*
Insomnia	3.6	3.7	3.2
Dizziness	3.5	3.4	4.2
Tooth disorder	2.9	4.3*	4.4*
Pharyngitis	2.9	2.7	3.5
Urinary tract infection	2.8	1.8*	3.0
Vomiting	2.6	3.5	2.7
Hypertension	2.0	2.0	3.1*
Constipation	2.2	6.8*	6.5*
SGPT increased	1.0	5.1*	1.2
SGOT increased	0.9	4.3*	1.0

Data represent percentages of patients.
*p<0.05 vs. celecoxib 400 mg BID.

Table 5.b displays the most common adverse events causing withdrawal in the study. The overall incidence of withdrawal due to an adverse event was statistically significantly lower for celecoxib than for diclofenac. This difference is largely attributable to lower withdrawal rates for GI symptoms and hepatoxicity.

Table 5.b. Adverse Events Causing Withdrawal with Incidence ≥1% in Any Treatment Group: Entire Study Period

Adverse Event	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
Any event	22.4	26.5*	23.0
Abdominal pain	4.3	6.5*	4.9
Dyspepsia	3.8	4.4	3.9
Rash	2.1	0.7*	1.3*
Nausea	1.7	2.8*	1.8
Diarrhea	1.4	2.7*	0.8*
Flatulence	1.2	1.8	1.4
Gastric ulcer	0.3	0.7	1.0*
SGOT increased	0.1	2.1*	0.1
SGPT increased	0.1	2.3*	0.1
Hepatic function abnormal	<0.1	1.1*	<0.1

Data represent percentages of patients.
*p<0.05 vs. celecoxib 400 mg BID.

Adverse events that occurred after the first 90 days of the study were similar in nature to those occurring most commonly in the entire study. The incidences of most events declined over time, and thus there was no evidence of cumulative toxicity (i.e., duration-dependent toxicity).

5.2. Serious Adverse Events

Table 5.c summarizes serious adverse events in the CLASS trial. The highest rate for any serious adverse event was 0.8 per 100 patient-years, seen in at least one treatment group for myocardial infarction, coronary artery disorder, accidental fracture, cardiac failure, and back pain. The incidences did not suggest any important differences among the treatment groups. These serious adverse events reflect common causes of morbidity in the arthritis patient population.

Table 5.c. Summary of Serious Adverse Events: Entire Study Period

Adverse Event	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
Patient-years	2320.4	1080.5	1122.5
Any serious event	11.6	10.3	10.6
Abdominal pain	0.3	0.6	0.2
Accidental fracture	0.4	0.4	0.8
Accidental injury	0.1	0.4	0.6
[redacted]	Non-Resp.		
Back pain	0.6	0.3	0.8
[redacted]	Non-Resp.		
Cellulitis	0.3	<0.1	<0.1
[redacted]	Non-Resp.		
GI hemorrhage	0.3	0.2	<0.1
[redacted]	Non-Resp.		
Pneumonia	0.6	0.5	0.4
[redacted]	Non-Resp.		

Data represent number of patients (number per 100 patient-years). Table includes any event experienced by a total of at least 10 patients across the three treatment groups.

5.3. Deaths

A total of 16 deaths occurred during the study or during post-study follow-up (Table 5.d): 8 in the celecoxib 400 mg BID group, 5 in the diclofenac 75 mg BID group, and 3 in the ibuprofen 800 mg TID group. Adjustment for duration of exposure shows similar rates of deaths in the three treatment groups.

Table 5.d. Summary of Deaths Occurring During Treatment or Within 28 Days After Discontinuation of Treatment

Adverse Event*	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
[redacted]	Non-Resp.		
Accidental injury	1	-	-
[redacted]	Non-Resp.		
Sepsis	1	-	-
Carcinoma	1	-	-
[redacted]	Non-Resp.		
Total (No. per 100 pt-yr)	8 (0.34)	5 (0.46)	3 (0.27)

*For cases in which no adverse event preferred term is available, the event is classified by cause of death listed on the end-of-study CRF.

5.4. Clinical Laboratory Evaluations

Clinical laboratory results are presented as group mean values over time by treatment groups. Table 5.e summarizes the mean changes from Baseline to the Final Visit for each standard laboratory test performed during the study. Many differences among groups were statistically significant, owing to the large numbers of patients in each group. Changes in mean laboratory values that were noteworthy were those in liver function tests, for which the statistically significant differences represent the known hepatic effects of diclofenac; creatinine changes, for which the group mean increase was statistically significantly higher for diclofenac than for celecoxib; and differences between groups in hematocrit and hemoglobin changes.

Table 5.e. Mean Changes from Baseline to Final Visit in Laboratory Values

Laboratory Test	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Hemoglobin, g/dL	-0.06 (0.013)	-0.26 (0.020) *	-0.37 (0.019) *
Hematocrit	-0.001 (0.0004)	-0.007 (0.0006) *	-0.012 (0.0007) *
Platelet count, $x10^9$/L	-2.3 (0.70)	10.0 (1.11) *	7.9 (0.94) *
WBC, $x10^9$/L	-0.09 (0.029)	0.06 (0.038) *	0.01 (0.041) *
Total bilirubin, µmol/L	0.0 (0.05)	0.1 (0.06)	-1.0 (0.07) *
Alkaline phosphatase, U/L	0.9 (0.23)	1.6 (0.38) *	-0.5 (0.31) *
AST, U/L	0.3 (0.12)	5.0 (0.57) *	0.9 (0.16)
ALT, U/L	-0.2 (0.18)	11.6 (1.10) *	1.3 (0.24)
Creatine kinase, U/L	-2.0 (1.17)	1.3 (2.18)	-0.1 (1.97)
Creatinine, µmol/L	0.8 (0.22)	2.4 (0.33) *	1.5 (0.33)
BUN, mmol/L	0.66 (0.027)	0.58 (0.041)	0.52 (0.039) *
Sodium, mmol/L	-0.1 (0.05)	-0.4 (0.07) *	0.0 (0.07)
Potassium, mmol/L	0.05 (0.007)	0.03 (0.010)	-0.03 (0.010) *
Chloride, mmol/L	0.7 (0.05)	0.4 (0.07) *	0.7 (0.07)
Bicarbonate, mmol/L	0.2 (0.04)	0.3 (0.06)	0.1 (0.06) *
Inorganic phosphorus, mmol/L	0.009 (0.0030)	-0.012 (0.0042) *	-0.003 (0.0046)

Data represent mean (SE) changes from Baseline.
*p<0.05 vs. celecoxib 400 mg BID.

Mean changes from Baseline in the special iron-related laboratory tests are summarized in Table 5.f. These tests could have been performed at any time during the study but were only required by the protocol in the event of new-onset anemia. The decreases in iron and ratio of iron to iron-binding capacity in the NSAID groups are consistent with iron depletion, suggesting that the decreases seen in hematocrit and hemoglobin were secondary to occult GI blood loss.

Table 5.f. Mean Changes from Baseline to Final Visit in Special Laboratory Values

Laboratory Test	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
MCHC, g/L	-0.22 (0.060)	-0.30 (0.081)	0.01 (0.067) *
MCV, fL	0.4 (0.22)	1.4 (0.34) *	-0.2 (0.27)
Iron, µmol/L	0.5 (0.61)	-1.7 (0.61) *	-1.3 (0.52) *
Ferritin, pmol/L	13.56 (15.572)	62.38 (41.153)	-10.65 (8.418)
Iron-binding capacity, µmol/L	-2.51 (0.587)	-1.65 (0.654)	-0.65 (0.747) *
Ratio of iron to iron-binding capacity	0.014 (0.0116)	-0.026 (0.0120) *	-0.022 (0.0098) *

Data represent mean (SE) changes from Baseline.
*p<0.05 vs. celecoxib 400 mg BID.

5.5. GI Effects

The adverse events relating to the GI system were analyzed according to the two principal factors that affected the risk of developing an ulcer complication: six-month data versus the entire study period, and patients not taking aspirin versus those taking aspirin.

As seen in Table 5.g, the results at six months were similar to those for the entire study period. For the common GI adverse events, six-month incidences were all within 2% of the overall incidences, and this was also true for withdrawals due to GI adverse events. In all GI adverse event measures, celecoxib was better tolerated than diclofenac and generally similar to ibuprofen in tolerability. Almost all of the common GI adverse events were statistically significantly more frequent for diclofenac than for celecoxib.

Table 5.g. Summary of GI Adverse Events by Time Interval

Adverse Event	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
Entire Treatment Period			
Any GI event	**45.6**	**55.0 ***	**46.2**
Dyspepsia	16.5	19.5 *	16.5
Abdominal pain	11.7	18.5 *	11.3
Diarrhea	10.9	15.0 *	7.5 *
Nausea	8.2	12.1 *	9.0
Flatulence	7.3	11.4 *	7.2
Tooth disorder	2.9	4.3 *	4.4 *
Vomiting	2.6	3.5	2.7
Constipation	2.2	6.8 *	6.5 *
Any GI event causing withdrawal	**12.2**	**16.6 ***	**13.4**
First Six Months			
Any GI event	**40.3**	**49.9 ***	**40.5**
Dyspepsia	14.4	17.7 *	14.4
Abdominal pain	9.7	16.7 *	9.5
Diarrhea	9.4	13.6 *	6.0 *
Nausea	6.9	11.0 *	7.6
Flatulence	6.6	10.1 *	6.5
Tooth disorder	2.4	3.6 *	3.2
Vomiting	2.1	3.1 *	2.3
Constipation	1.7	5.9 *	5.9 *
Any GI event causing withdrawal	**10.8**	**15.5 ***	**12.0**

Data represent percentages of patients. Table includes any GI adverse event with incidence ≥3% in any treatment group.
* $p<0.05$ vs. celecoxib 400 mg BID.

The incidences of GI adverse events in patients not taking aspirin were similar to those in the overall population, though generally reduced by approximately 1% across treatment groups. The statistical relationships described above were maintained. In general, the use of aspirin increased incidences of GI adverse events across groups and attenuated some of the differences between celecoxib and the NSAIDs.

The occurrence of occult blood loss as indicated by decreases in hematocrit (>2 g/dL) and hemoglobin (≥10 points) represents an important adjunct measure of GI mucosal effects of NSAIDs. Table 5.h shows the percentages of patients who experienced an extreme decrease in hematocrit and/or hemoglobin, both in the overall population as well as in those patients who did not experience an ulcer complication, patients with OA or RA, and patients taking or not taking aspirin. The proportions of patients receiving diclofenac or

ibuprofen who had extreme decreases in hematocrit and/or hemoglobin were consistently higher than in patients receiving celecoxib.

Table 5.h. Summary of Hemoglobin/Hematocrit Contingency Tables: Entire Study Period

Patients with hemoglobin decrease >2 g/dL and/or hematocrit decrease ≥0.10	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
All patients	87/3701 (2.4)	82/1849 (4.4)	102/1802 (5.7)
Excluding ulcer complications	83/3682 (2.3)	81/1840 (4.4)	95/1792 (5.3)
Excluding ulcer complications/ Ulcers	82/3659 (2.2)	78/1824 (4.3)	93/1768 (5.3)
Excluding ulcer complications/ Ulcers/non-ulcer complications	73/3545 (2.1)	68/1753 (3.9)	81/1693 (4.8)
Excluding ulcer complications/ Ulcers/non-ulcer complications/negatives	41/3068 (1.3)	41/1490 (2.8)	42/1364 (3.1)
OA patients	63/2675 (2.4)	48/1340 (3.6)	74/1299 (5.7)
RA patients	24/1026 (2.3)	34/509 (6.7)	38/503 (5.6)
Patients not taking aspirin	53/2864 (1.9)	53/1428 (3.7)	73/1414 (5.2)
Patients taking aspirin	34/837 (4.1)	24/421 (6.9)	29/388 (7.5)

Data represent number/total (percentage) of patients who met the criterion in Column 1.

5.6. Renal Effects

Patients receiving ibuprofen experienced more edema (peripheral and generalized) and hypertension (new-onset and aggravated) than celecoxib or diclofenac patients. In three of these four categories the differences were statistically significant between celecoxib and ibuprofen (Table 5.i).

Table 5.i. Summary of Selected Adverse Events Relating to Renal Function: Entire Study Period

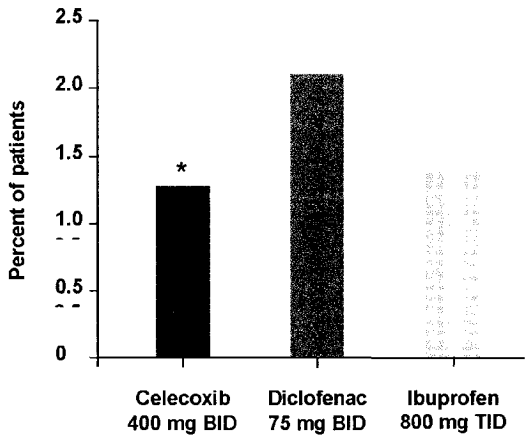
Adverse Event	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)
Hypertension	2.0	2.0	3.1*
Hypertension aggravated	0.8	0.6	1.2
Edema generalized	0.5	0.6	1.0*
Edema peripheral	3.7	3.5	5.2*
Cardiac failure	0.3	0.2	0.5
BUN increased	1.1	1.7	0.9
NPN increased	1.3	1.9	1.2
Renal failure acute	0.0	<0.1	0.0
Renal function abnormal	<0.1	<0.1	0.1

Data represent percentages of patients.
*p<0.05 vs. celecoxib 400 mg BID.

Adverse events relating to increases in renal function laboratory values (BUN increased and NPN increased) were more frequent for diclofenac than for celecoxib. The differences were statistically significant when examined in the six-month analysis.

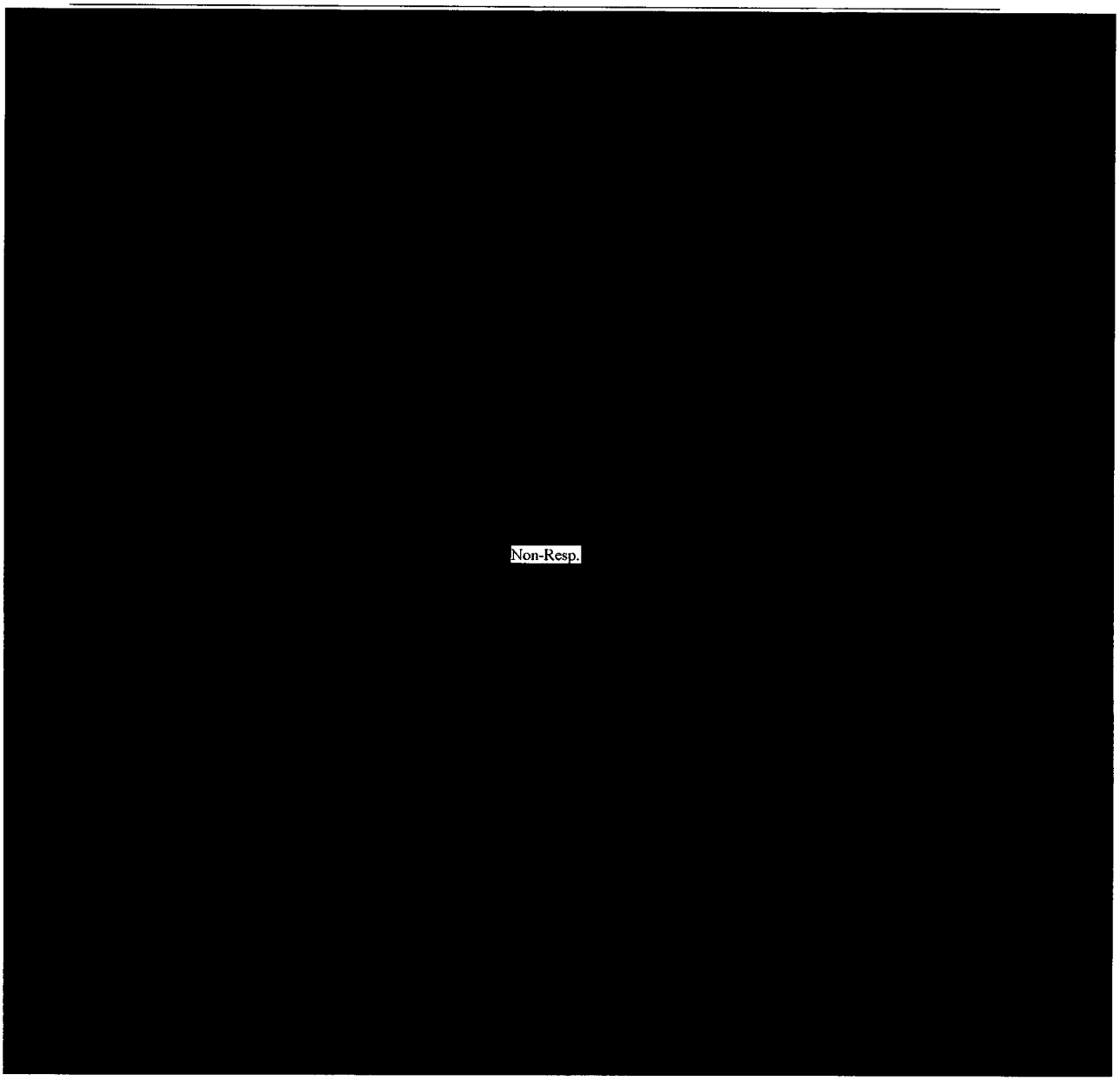
When lower thresholds of 159 μmol/L for extreme creatinine and 14.3 mmol/L for extreme BUN were used in the laboratory analyses, incidences of either an extreme BUN or extreme creatinine value were 1.3% for celecoxib, 2.1% for diclofenac, and 1.4% for ibuprofen. The difference between celecoxib and diclofenac was statistically significant (Figure 5.a).

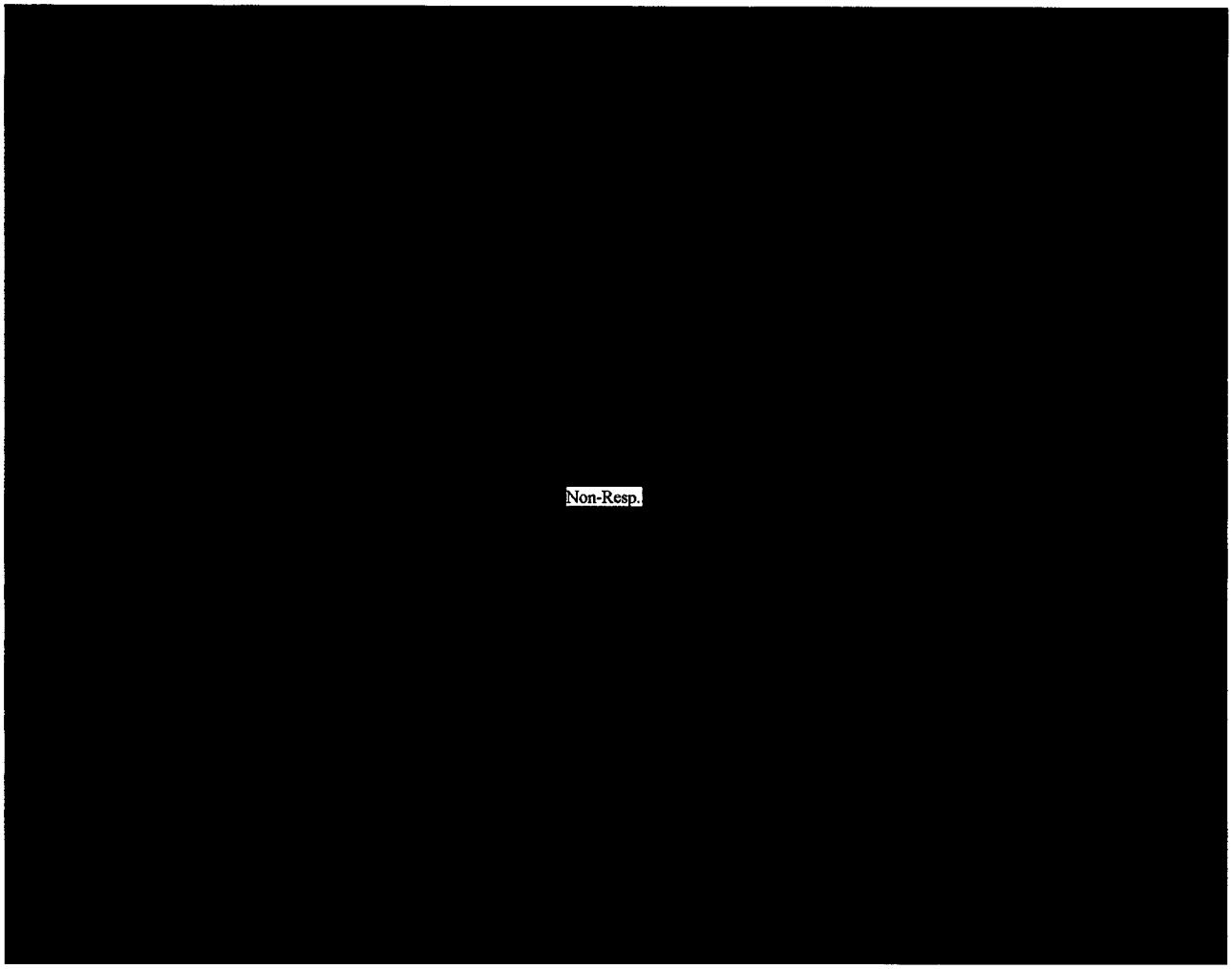
Figure 5.a. **Incidences of Extreme Values in BUN (≥14.3 mmol/L) and/or Creatinine (≥159 µmol/L)**



*p<0.05 vs. diclofenac

[redacted]
Non-Resp.


Non-Resp.



5.6.2. Hepatobiliary Effects

Celecoxib had no laboratory or adverse event results suggestive of a hepatic effect. As previously reported (28,29), diclofenac was associated with increases in hepatic transaminases. A consistent pattern of enzyme elevation was seen in diclofenac patients, indicated by group mean changes in AST and ALT values, and the occurrence of extreme elevations in individual patients. The clinical significance of these elevations is indicated by adverse event data: approximately half of diclofenac patients for whom liver enzyme elevations were reported as adverse events were consequently withdrawn from the study (Table 5.1).

Table 5.l. Adverse Events and Laboratory Values Related to Hepatic Function: Entire Study Period

Parameter	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Adverse Events			
SGOT increased	0.9	4.3*	1.0
SGPT increased	1.0	5.1*	1.2
Hepatic function abnormal	0.3	1.6*	0.3
Adverse Events Causing Withdrawal			
SGOT increased	0.1	2.1*	0.1
SGPT increased	0.1	2.3*	0.1
Hepatic function abnormal	<0.1	1.1*	<0.1
Extreme Laboratory Values			
SGPT (ALT) ≥3 x ULN	0.3	3.6	0.6

Data represent percentages of patients.
*p<0.05 vs. celecoxib 400 mg BID.

5.6.3. Dermatologic Effects

In this study, the incidence of rash was statistically significantly higher for celecoxib than for either diclofenac or ibuprofen as previously shown in Table 5.a. The incidence of pruritus was statistically significantly higher for celecoxib than for ibuprofen (2.4% vs. 1.4%, p=0.009). Generally, drug-related rash and pruritus would be expected to occur within the first 28 days of treatment; this analysis is shown in Table 5.m. For celecoxib, most cases of rash or pruritus within the first 28 days (~90%) were mild or moderate.

Table 5.m. Characteristics of Rash and Pruritus Among Treatment Groups Within First 28 Days of Treatment

Parameter	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Rash			
Overall incidence	3.7	1.2*	1.1*
Causing withdrawal	1.9	0.5*	0.5*
Pruritus			
Overall incidence	1.7	1.1	0.8*
Causing withdrawal	0.7	0.3	0.2*

Data represent percentages of patients.
*p<0.05 vs. celecoxib 400 mg BID.

No serious dermatologic adverse events occurred in patients receiving celecoxib. Only three serious adverse events relating to skin occurred: two skin ulcerations (one each occurring in the diclofenac and ibuprofen groups) and one skin disorder in the ibuprofen group.

5.7. General Safety Conclusions

The data from the CLASS study support the following conclusions for celecoxib 400 mg BID:

- No quantitative or qualitative changes were noted in the safety profile of celecoxib compared with that seen in previous celecoxib trials; specifically, no dose- or duration-dependent toxicity was observed.
- Celecoxib is associated with a diminished incidence of chronic decreases in hematocrit and hemoglobin, presumptively due to GI blood loss, compared with conventional NSAIDs.
- Celecoxib is associated with improved GI tolerability relative to diclofenac.
- Celecoxib is associated with a diminished incidence of edema and hypertension relative to ibuprofen.
- Celecoxib is associated with a diminished incidence of clinically significant changes in BUN and creatinine compared with diclofenac.
- Celecoxib is associated with a diminished incidence of clinically significant changes in liver function tests compared with diclofenac.
- No difference in the incidence of thromboembolic cardiovascular events was seen between celecoxib and conventional NSAIDs.
- Celecoxib is associated with increased incidences of nonserious drug-related rash and pruritus compared with ibuprofen and diclofenac.

6. SAFETY UPDATE FROM THE OPEN-LABEL SAFETY TRIAL

The long term safety trial, Study 024, is an additional source of safety information on the effects of celecoxib in OA and RA patients that can be used to place the CLASS results into context. (This study has recently been completed, and a final report is in preparation.) This study more closely approximates clinical practice than the controlled celecoxib trials in that drug treatment was not blinded and the dose of celecoxib could be titrated by the physician; however, the rigor of a clinical trial was maintained in terms of the collection of adverse events. The principal limitation of the data is that patients with significant medical problems excluded from the original controlled arthritis trials were not eligible to enroll in Study 024.

There was a higher number of younger patients with RA compared to patients with OA, in the long-term open-label trial. The mean age for RA patients was 54.9 years compared to 61.6 years for OA patients. There were similar distributions in ethnicity and gender for each group. Doses of celecoxib permitted in the study ranged from 100-400 mg BID. The doses used were typically higher than those currently recommended for OA and RA, but were on average lower than in the CLASS study: the average daily doses for OA and RA patients were 329 mg and 605 mg, respectively, or approximately 50% greater than the maximum effective dose for the respective indications. This trial provides approximately 7000 additional patient-years of exposure from which the safety of celecoxib can be assessed in a rigorous fashion.

As shown in Table 6.a, the incidences and types of adverse events from the long-term open-label trial were similar to those observed in the CLASS trial.

Table 6.a. Adverse Events with Incidence ≥3% in Celecoxib Patients: CLASS Trial and Long-term Open-label Trial (Study 024)

Adverse Event	CLASS Trial: Celecoxib 400 mg BID (N=3987)	Study 024: Celecoxib 100-400 mg BID (N=5157)
Any event	81.8	86.3
Dyspepsia	16.5	13.1
URTI	15.4	22.3
Headache	13.9	17.9
Abdominal pain	11.7	8.4
Diarrhea	10.9	10.0
Sinusitis	8.8	13.0
Nausea	8.2	7.3
Flatulence	7.3	3.2
Rash	6.2	5.5
Influenza-like symptoms	5.4	5.4
Injury accidental	5.3	11.7
Anemia	4.4	3.6
Coughing	4.4	5.6
Rhinitis	4.3	5.1
Bronchitis	4.0	7.2
Back pain	3.7	7.2
Edema peripheral	3.7	6.0
Insomnia	3.6	5.4
Dizziness	3.5	5.8
Pharyngitis	2.9	4.3
Tooth disorder	2.9	4.8
Urinary tract infection	2.8	5.4
Gastroesophageal reflux	2.7	3.2
Pain	2.6	3.7
Arthralgia	2.3	3.3
Constipation	2.2	3.0
Hypertension	2.0	4.2
Gastroenteritis	1.9	3.5
Neuralgia	1.8	3.6
Myalgia	1.7	3.5
Depression	1.6	3.3
Fatigue	1.6	3.3
Chest pain	1.3	3.1
Fracture accidental	1.3	3.3
Prostatic disorder	1.2	3.0

Derived from Celecoxib Integrated Summary of Benefits and Risks (Document No. N49-00-07-842). Data represent percentages of patients.

In general, incidence rates tended to be somewhat higher in Study 024 because of the longer duration of exposure. The higher incidence of GI symptoms in the CLASS trial may reflect the more intense surveillance for GI events in this study.

The most common serious adverse events that occurred in Study 024 are summarized in Table 6.b. In general, the incidences and types of serious adverse events between these

two studies closely approximate one another and represent common causes of morbidity in the arthritis patient population.

Table 6.b. Serious Adverse Events in Celecoxib Patients: CLASS Trial and Long-term Open-label Trial (Study 024)

Adverse Event	CLASS Trial: Celecoxib 400 mg BID (N=3987)	Study 024: Celecoxib 100-400 mg BID (N=5157)
Patient -years	2320.4	6965.3
Any serious event	11.6	9.8
[redacted] Non-Resp.		
Back pain	0.6	0.5
Pneumonia	0.6	0.4
[redacted] Non-Resp.		
Accidental fracture	0.4	0.4
[redacted] Non-Resp.		
Cellulitis	0.3	0.2
[redacted] Non-Resp.		
Abdominal pain	0.3	0.1
Breast neoplasm malignant	0.2	0.2
[redacted] Non-Resp.		
Cholecystitis	0.2	0.2
Accidental injury	0.1	0.3
Urinary incontinence	0.1	0.2
Carcinoma	<0.1	0.3
Cholelithiasis	<0.1	0.2
Hernia	<0.1	0.2
Implantation complication	<0.1	0.2
Basal cell carcinoma	0.0	0.3
[redacted] Non-Resp.		
Skin carcinoma	0.0	0.2

Derived from Celecoxib Integrated Summary of Benefits and Risks (Document No. N49-00-07-842). Data represent number per 100 patient-years. Table includes any event experienced by a total of at least 10 patients in either study.

6.1. GI Safety

The final overall annualized incidence of ulcer complications in Study 024 was 0.23 per 100 patient-years (a total of 16 events over 6965.3 patient-years of exposure). The rate of ulcer complications in Study 024, while similar to that derived during the NDA, is lower than that observed in the CLASS trial over six months (0.77 per 100 patient-years), attributable to the difference in aspirin use between the two studies (approximately 14% in Study 024 vs. 22% in the CLASS trial) and reinforcing the notion that aspirin is an independent cause of ulcers for patients on celecoxib. Ulcer complications in 5 of the 16 cases occurred among patients on low-dose aspirin.

6.2. Renal, [redacted], Hepatic, and Dermatologic Effects

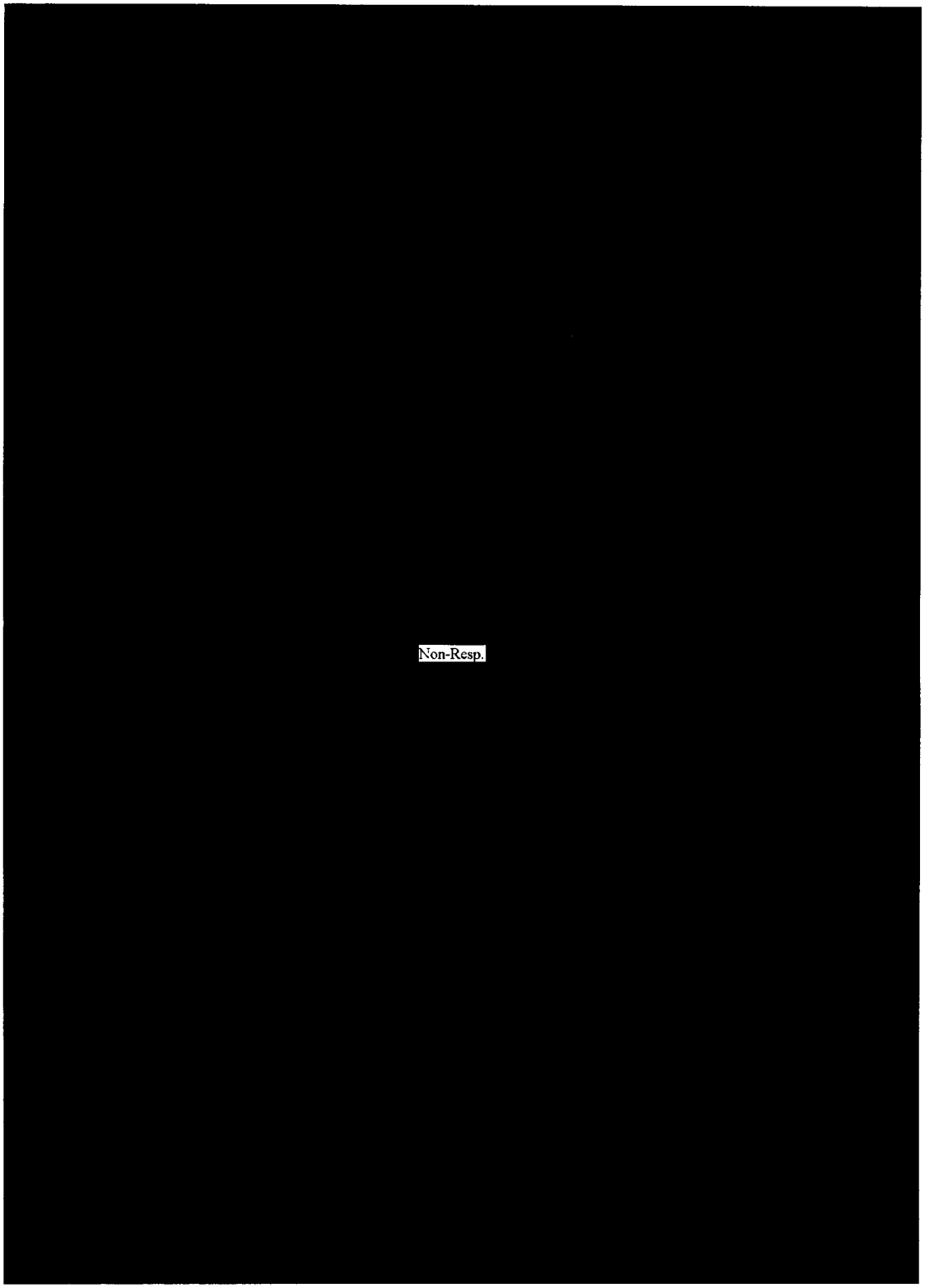
The incidences of selected renal adverse events occurring in the CLASS and long-term open-label trials are shown in Table 6.c. In general, the incidence rates of adverse events were lower in the CLASS trial compared to the long-term open-label trial. There was a slightly higher incidence of BUN and NPN increased; however, this difference was associated with no adverse event of acute renal failure. The higher incidence of adverse events in the long-term open-label study is most likely due to longer duration of exposure.

Table 6.c. Summary of Selected Adverse Events Relating to Renal Function: CLASS Trial and Long-Term Open-label Trial (Study 024)

Adverse Event	CLASS Trial: Celecoxib 400 mg BID (N=3987)	Study 024: Celecoxib 100-400 mg BID (N=5157)
[redacted]		
Edema generalized	0.5	0.9
Edema peripheral	3.7	6.0
[redacted]		
BUN increased	1.1	0.6
NPN increased	1.3	0.7
Renal failure acute	0.0	<0.1
Renal function abnormal	<0.1	0.1

Derived from Celecoxib Integrated Summary of Benefits and Risks (Document No. N49-00-07-842).
Data represent percentages of patients.

The incidences of selected serious renal adverse events from Study 024 compared to the CLASS trial are shown in Table 6.d. These data show that serious renal adverse events associated with supratherapeutic doses of celecoxib are generally rare. The most common serious renal-related adverse event, cardiac failure, occurred with an annualized incidence of 0.3% on celecoxib (CLASS trial and Study 024 combined) versus an annualized incidence of 0.5% on conventional NSAIDs pooled from the CLASS trial.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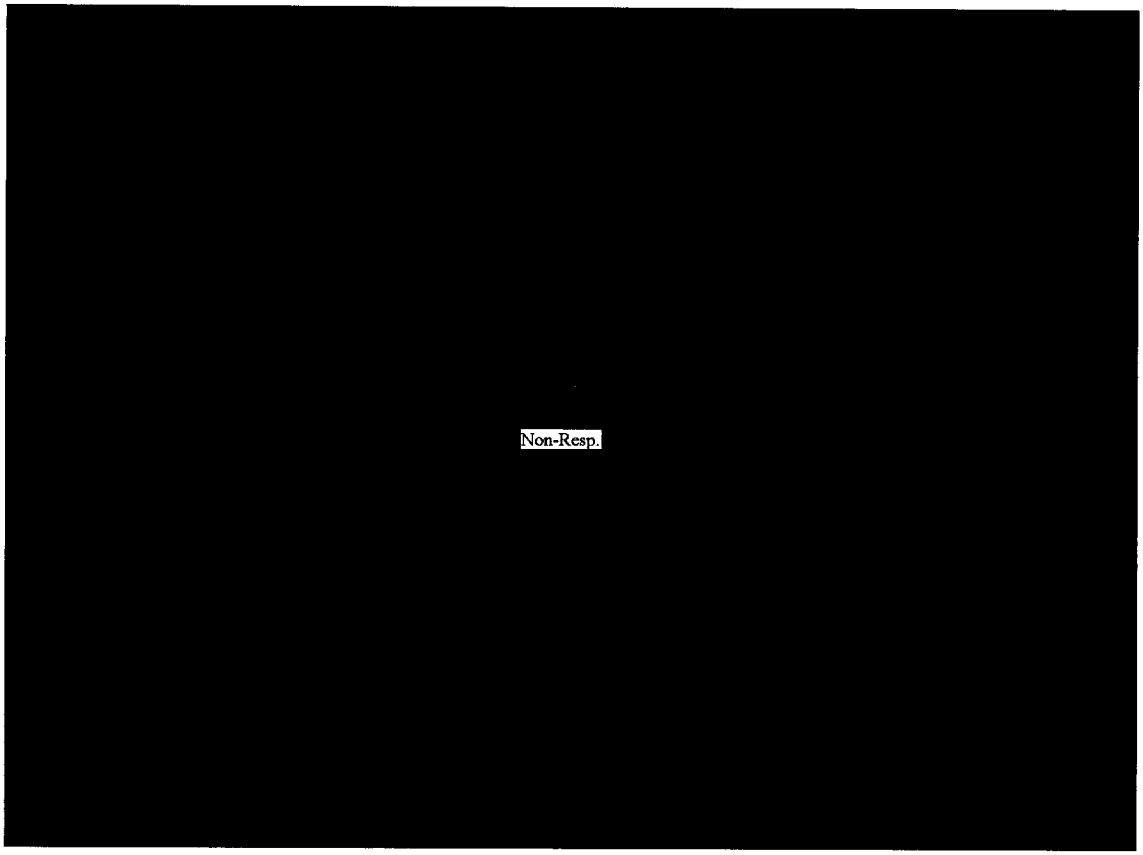


Table 6.g. Incidences of Selected Dermatologic Adverse Events: CLASS Trial and Long-term Open-label Trial (Study 024)

Adverse Event	CLASS Trial: Celecoxib 400 mg BID (N=3987)	Study 024: Celecoxib 100-400 mg BID (N=5157)
Angioedema	<0.1	0.0
Bullous Eruption	<0.1	0.1
Photosensitivity Reaction	0.1	0.3
Pruritus	2.4	2.9
Rash	6.2	5.5
Urticaria	0.7	0.9

Derived from Celecoxib Integrated Summary of Benefits and Risks (Document No. N49-00-07-842).
Data represent percentages of patients.

No serious skin-related adverse events occurred in patients receiving celecoxib in the CLASS trial. In Study 024, serious dermatologic events were pruritus, basal cell carcinoma, malignant melanoma, skin carcinoma, and skin ulceration.

The incidences of adverse events related to hepatic function occurring in the CLASS and long-term open label trials are shown in Table 6.h. The incidences of these adverse events were low and similar in the CLASS and long-term open-label trials.

Table 6.h. Incidences of Hepatic-Related Adverse Events: CLASS Trial and Long-term Open-label Trial (Study 024)

Laboratory Test	CLASS Trial: Celecoxib 400 mg BID (N=3987)	Study 024: Celecoxib 100-400 mg BID (N=5157)
SGOT increased	0.9	1.0
SGPT increased	1.0	1.3
Hepatic function abnormal	0.3	0.3

Derived from Celecoxib Integrated Summary of Benefits and Risks (Document No. N49-00-07-842).
Data represent percentages of patients.

A total of four hepatic serious adverse events occurred in celecoxib patients in the two trials: one case of hepatic cirrhosis in the CLASS trial, one case of hepatitis in each of the trials, and one case of cholestatic hepatitis in the CLASS trial.

6.3. Safety Conclusions for Study 024

The safety data for Study 024 indicate the following:

- Overall, adverse events were generally lower in the CLASS trial compared to the long-term open-label trial.
- The serious adverse event rates were similar between the CLASS and long-term open-label trials, and represent common causes of morbidity in the study population.
- The rate of ulcer complications in the long-term open-label trial was similar to that reported in the NDA and lower than that observed in the CLASS trial. This difference is attributable to the increased aspirin use in the CLASS trial.
- Review of renal [redacted] Non-Resp. hepatic and dermatologic adverse events revealed generally lower incidences of these types of adverse events in the CLASS trial compared to the long-term open-label trial.

7. POSTMARKETING SURVEILLANCE SUMMARY

7.1. General Safety

Postmarketing surveillance provides safety information that can also be used to put the results of the CLASS study into context. Such surveillance takes place under clinical practice conditions; however, the rigor and assiduousness of safety data collection is not comparable to that in clinical trials. Moreover, reporting rates are crude estimates of incidence rates, the precision of the estimate varying as a function of the severity and rarity of the event. Despite these qualifications, the incidence of rare serious adverse events (annualized incidence of less than one per 10,000 patient-years) can be estimated from this database.

The most commonly reported serious adverse events were GI in nature. The incidence of serious GI adverse events relating to ulcer complications was 19.9/100,000 patient-years (or 0.02% per 100 patient-years). The overall rate of serious GI events relating to ulcer complications was approximately ≥10-fold lower than the corresponding rates of such events derived from celecoxib clinical trials. Although it is difficult to estimate the degree of underreporting of such events during postmarketing surveillance, this rate appears consonant with the clinical trial experience.

Although quantitative analysis of GI mortality risk is not possible, qualitative analysis shows that of the 30 fatal GI events noted during 1999, most occurred in elderly patients with substantial comorbidities.

For serious renal, [redacted] Non-Resp. hepatic, and dermatologic adverse events, postmarketing reporting rates were in general low (less than three per 100,000 patient-years). Of specific note, the incidence of acute renal failure (too low to be estimated during clinical trials) was 3.9 per 100,000 patient-years during postmarketing surveillance.

7.2. Rare Serious Adverse Events

To date, postmarketing surveillance reports have shown the occurrence of a number of rare serious adverse events. These events, and the reporting rates for the first year of postmarketing based on approximately 6.8 million treated patients and 1.8 million patient-years of exposure, are summarized in Table 7.a.

Table 7.a. Rare Serious Adverse Events Reported During Postmarketing Surveillance: December 31, 1998 through December 31, 1999

Event	Reporting Rate (Number per 100,000 Patient-Years)
Non-Resp.	
Liver and biliary	
Hepatitis	0.5
Jaundice	1.5
Hepatic failure	0.4
Hemic and lymphatic	
Agranulocytosis	0.2
Aplastic anemia	0.3
Pancytopenia	0.4
Leukopenia	0.9
Metabolic	
Hypoglycemia	0.4
Renal	
Interstitial nephritis	0.2
Skin	
Erythema multiforme	0.3
Exfoliative dermatitis	0.2
Stevens-Johnson syndrome	0.3
Epidermal necrolysis	0.1
General	
Anaphylactoid reaction	1.1
Angioedema	1.9

The events listed in Table 7.a have been added to the "Adverse Reactions" section of the celecoxib product label. (8) No significant trends and no new medical issues have been since noted.

8. CONCLUSIONS

The safety data from the CLASS trial, the original NDA studies, the long-term open-label safety study (Study 024) encompassing 10,000 patient-years of exposure to celecoxib, and postmarketing surveillance (encompassing 1.8 million patient-years of exposure to celecoxib) support the following conclusions:

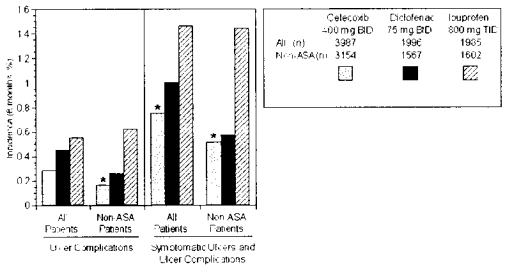
- Celecoxib at a supratherapeutic dose for OA and RA is associated with a lower rate of symptomatic ulcers and/or ulcer complications relative to conventional NSAIDs at therapeutic doses.
- Celecoxib is safe and well tolerated at doses four-fold and two-fold greater than those required for maximal efficacy in OA and adult RA, respectively.
- Celecoxib is not associated with dose- or duration-related increases in adverse effects.
- Celecoxib at a supratherapeutic dose is associated with less frequent clinically relevant changes in hemoglobin or hematocrit than conventional NSAIDs at therapeutic doses.
- Celecoxib at a supratherapeutic dose generally exhibits better GI tolerability than conventional NSAIDs at therapeutic doses.
- Celecoxib at a supratherapeutic dose is associated with lower incidences of common renal and hepatic adverse events than conventional NSAIDs at therapeutic doses.

[redacted]
Non-Resp.

9. PROPOSED LABELING SECTION

CLINICAL STUDIES	
ORIGINAL LABEL	**PROPOSED LABEL CHANGES BASED ON CLASS**
	Special Studies ***Long Term Outcome Study:*** The incidence of symptomatic GI ulcers and serious ulcer complications (bleeding, perforation or obstruction) was prospectively studied in approximately 5800 OA patients and 2200 RA patients. Patients received CELEBREX 400 mg BID (4-fold and 2-fold greater than the recommended OA and RA doses, respectively) or diclofenac 75 mg BID or ibuprofen 800 mg TID (common therapeutic doses). Approximately 22% of patients were on low dose aspirin (ASA) for cardiovascular disease prophylaxis. In the overall population CELEBREX was associated with a significantly lower incidence of symptomatic GI ulcers and ulcer complications vs. ibuprofen. In patients not taking low dose aspirin (non-ASA) a significantly lower incidence of ulcer complications vs. ibuprofen was observed (Figure 2). The incidence rates for diclofenac may be underestimated because of a higher incidence of early withdrawals due to GI adverse events than CELEBREX and ibuprofen.

Figure 2:
Incidence of Symptomatic Ulcers and Ulcer Complications



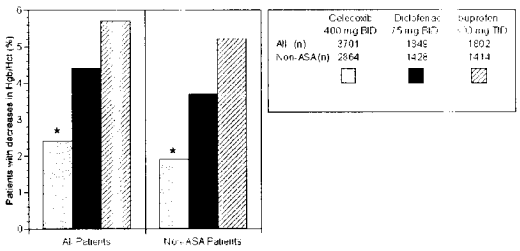
*p<0.05 vs. ibuprofen

CELEBREX (4-fold and 2-fold greater than the recommended OA and RA doses, respectively) was also associated with a significantly lower incidence of clinically relevant decreases in hemoglobin (> 2 g/dl) or hematocrit (\$10 points) than ibuprofen and diclofenac. (Figure 3). The pooled rates from other controlled arthritis trials (1 to 6 months duration, most of 3 months duration) were 0.4%, 0.9%, and 2.8% in placebo, celecoxib, and comparator NSAID groups, respectively. Celecoxib doses ranged from 50mg bid to 400mg bid.

The incidence of clinically relevant decreases in hemoglobin and hematocrit in CELEBREX patients was not affected by aspirin use.

The correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established. Serious clinically significant upper GI bleeding has been observed in patients receiving CELEBREX in controlled and open-labeled trials, albeit infrequently (see WARNINGS-Gastrointestinal [GI] Effects). Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking CELEBREX vs. comparator NSAID products have not been performed.

Figure 3:
Incidence of Clinically Relevant Decreases in Hemaglobin and/or Hematocrit



*p<0.05 vs. ibuprofen and diclofenac

Approximately 22% of patients enrolled in the long term outcome study were taking aspirin (≤325 mg/day). In the CELEBREX patients the rate of ulcers and ulcer complications was higher in aspirin than in non-aspirin users.

GI WARNING	
ORIGINAL LABEL	**PROPOSED LABEL CHANGES BASED ON CLASS**
Gastrointestinal (GI) Effects- Risk of GI Ulceration, Bleeding, and Perforation: ~~Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.~~	Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach or intestine has been observed in patients treated with CELEBREX albeit infrequently. Physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms.

~~It is unclear, at the present time, how the above rates apply to CELEBREX (see CLINICAL STUDIES-Special Studies).~~ Among 5,285 patients who received CELEBREX in controlled clinical trials of 1 to 6 months duration (most were 3 month studies) at a daily dose of 200 mg or more, 2 (0.04%) experienced significant upper GI bleeding, at 14 and 22 days after initiation of dosing. Approximately 40% of these 5,285 patients were in studies that required them to be free of ulcers by endoscopy at study entry. Thus it is unclear if this study population is representative of the general population. ~~Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking CELEBREX vs. comparator NSAID products have not been performed.~~	
~~NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.~~	In a prospective randomized controlled long term outcome trial in 8000 OA and RA patients in which low dose aspirin use was allowed, approximately 0.28% of patients on CELEBREX 400 mg BID demonstrated upper GI ulcer complications (bleeding, obstruction, or perforation) over 6 months (see Special Studies: Long term Outcome Study). In the absence of low dose aspirin use the rate was 0.16%. Patients most at risk of developing an ulcer complication were the elderly (≥ 75 years), patients in poor health or with cardiovascular disease, aspirin users and patients with a history of a GI ulcer or UGI bleeding.

	Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk of an ulcer complication, the lowest effective dose should be used.**
~~Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.~~	

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Volume/Page No.

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EXHIBIT 184

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Pharmacia Corp. †§ (PHA-$56.13) - Attractive

FDA Unlikely to Improve Celebrex Label

Data

Long-Term Growth	20%	Target Price	$60	Dividend/Yield	0.9%
Top-Line Growth	13%	S&P 500 P/E	22.2 x	Shares Out	1,286
Bottom-Line Growth	20%	Avg Group P/E	27.9x	Market Cap (MM)	$72,183
LT Debt to Tot Cap	44%	52-Wk Range	$61 - $34	Book Value	$8.63

Key Points

*** The FDA Arthritis Advisory Committee did not recommend a change in the current Celebrex label. PHA/PFE submitted data from the recently completed 8,000 patient CLASS trial, in which they hoped to demonstrate a clear safety advantage over traditional NSAIDs (ibuprofen and diclofenac), and have the traditional NSAID gastrointestinal side effect warning diminished or removed.

*** In reviewing Celebrex, consensus among the Advisory Panel members was that PHA/PFE's Celebrex did not establish a "meaningful safety advantage" in comparison to NSAIDs (ibuprofen and diclofenac). With the data available, the committee could not justify a change in Celebrex's label.

*** The Panel clearly expressed concern about the trend toward increased cardiovascular (CV) adverse events (heart attacks, unstable angina and strokes), a debate which should intensify in tomorrow's Advisory panel meeting for MRK's Vioxx (see MRK First Call note 2/7/01). During the rhetoric, members discussed the potential role that COX-2 inhibition could play in respect to CV events. Because Vioxx has a less favorable CV side effect profile, the possibility exists that a warning, informing physicians of the CV risk, could be added to Vioxx's label. A negative Vioxx label revision would provide PHA/PFE a major competitive marketing advantage.

*** Celebrex and the COX-2 family remains an important driver of Pharmacia's and to a lesser extent Pfizer's (smaller percentage of total revenues) growth. Although script growth in the US is moderating somewhat, increasing international sales should grow much more rapidly as new launches occur. In addition, paracoxib, an injectable COX-2 for pain management, was recently filed and should be approved into an $820 million worldwide market in Oct. 2001. Furthermore, valdecoxib, its second-generation product, is expected to be filed in the first half of 2001.

*** Assuming that both Celebrex and Vioxx's GI warning remains unchanged, there is little commercial implication, in our view. We believe that physician's widely view Celebrex as safer than traditional NSAIDs. For this reason, at *this time we are maintaining our sales estimates of $2.5 billion and $3.2 billion in 2000 and 2001, respectively, and* believe that the COX-2 inhibitor category will grow to more than $10 billion by 2005. That being said, clearly, the outcome of tomorrow's Advisory Panel meeting could have a dramatic effect on the landscape of the COX-2 inhibitor market, and therefore, our Celebrex estimates. (Please see below for possible outcomes) Reiterate $60 Price Target.

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	Earnings Estimates					P/E
	Q1 Mar	Q2 Jun	Q3 Sep	Q4 Dec	Year	Year
1999	$0.26	$0.40	$0.21	$0.24	$1.11	50.6x
2000	$0.33	$0.47	$0.33	$0.32	$1.45	38.7x
2001					$1.75	32.1x

The FDA Arthritis Advisory Committee will not recommend a change in the current Celebrex label. PHA/PFE submitted data from the recently completed 8,000 patient CLASS trial, in which they hoped to demonstrate a clear safety advantage over traditional NSAIDs (ibuprofen and diclofenac), and have the traditional NSAID gastrointestinal side effect warning diminished or removed.

In reviewing Celebrex, consensus among the Advisory Panel members was that PHA/PFE's Celebrex did not establish a "meaningful safety advantage" in comparison to NSAIDs (ibuprofen and diclofenac). With the data available, the committee could not justify a change in Celebrex's label. Although not statistically significant, the studies demonstrated trends toward decreased GI side effects and trends toward increased cardiovascular (CV) side effects. As a result, the panel will recommend further studies to firmly establish the relationship between Celebrex and aspirin as well as quantify the cardiovascular effects if any.

The Panel clearly expressed concern about the trend toward increased CV adverse events (heart attacks, unstable angina and strokes). During the rhetoric, members discussed the potential role that COX-2 inhibition could play in respect to CV events. We expect the debate over the cardiovascular side effect profile of COX-2 inhibitors to intensify in tomorrow's Advisory Panel meeting for MRK's Vioxx. Because Vioxx has a less favorable CV side effect profile, the possibility exists that a warning, informing physicians of the CV risk, could be added to Vioxx's label. A negative Vioxx label revision would provide PHA/PFE a major competitive marketing advantage.

That being said, the possibility exists, however unlikely, that the FDA could take an ultra-conservative approach and apply a CV warning to all COX-2 inhibitors (similar to the NSAID class warning) until proven otherwise. Such a warning could have an impact on the competitive dynamics of the anti-inflammatory market

Celebrex and the COX-2 family remains an important driver of Pharmacia's and to a lesser extent Pfizer's (smaller percentage of total revenues) growth. Although script growth in the US is moderating somewhat, increasing international sales should grow much more rapidly as new launches occur. In addition, paracoxib, an injectable COX-2 for pain management, was recently filed and should be approved into an $820 million worldwide market in Oct. 2001. Furthermore, valdecoxib, its second-generation product, is expected to be filed in the first half of 2001.

Assuming that both Celebrex and Vioxx's GI label remains unchanged, there is little commercial implication, in our view. It is important to note that the Panel did not claim that Celebrex was not safer than NSAIDs, just that the study did not statistically prove its enhanced safety profile. We believe that physician's widely view Celebrex as safer than traditional NSAIDs. For this reason, at this time we are maintaining our sales estimates of $2.5 billion and $3.2 billion in 2000 and 2001, respectively, and believe that the COX-2 inhibitor category will grow to more than $10 billion by 2005.

However, clearly, the outcome of tomorrow's Advisory Panel meeting could have a dramatic effect on the landscape of the COX-2 inhibitor market, and therefore, our Celebrex estimates. Possible outcomes include:

Celebrex no change in GI warning and

1) Vioxx no change in GI warning or CV warning – no impact to estimates
2) Vioxx improvement in GI warning and no change in CV warning – slight negative for Celebrex
3) Vioxx improvement in GI warning and a new CV warning – positive for Celebrex
4) Vioxx no change in GI warning but a new CV warning – positive for Celebrex

As stated above, the FDA could impose a class warning on all COX-2 inhibitors (similar to the standard NSAID class warning) which would change the competitive dynamics of the anti-inflammatory market.

Financial Importance of COX-2 Drugs for Respective Companies ($US mil)

Company	Drug	2000 Est.	2001 Est.	2002 Est.
Pharmacia	Celebrex	$2,571	$3,200	$3,600
% Pharma Revenues		*20.2%*	*22.8%*	*23.5%*
Pfizer	Celebrex	1,000	1,260	1,470
% Pharma Revenues		*4.4%*	*4.9%*	*5.0%*
Merck	Vioxx	2,160	3,460	4,100
% Pharma Revenues		*10.7%*	*15.4%*	*17.1%*

Companies Mentioned:
PHA, PFE, MRK

§ **PNU, MTC:** Within the past three years, Bear Stearns & Co. Inc. or one of its affiliates was the manager (co-manager) of a public offering of securities of this company and/or has performed, or is performing, other banking services, including acting as financial advisor, for which it has received a fee.
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EXHIBIT 185

Morning Meeting Note

The Investext Group

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PHA: No Change Recommended for Celebrex Labeling - Pt1 FBC

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No Change Recommended for Celebrex Labeling: "Status Quo" Mildly Disappointing , but Manageable

Summary

The FDA Arthritis Advisory Committee recommended no change in Celebrex's label during discussions Wednesday. This labeling posture resulted from statistical complications within the CLASS clinical trial, including Celebrex's failure to achieve a statistically significant improvement in its complicated ulcer primary endpoint and FDA requests for further study on the effects of COX-2 in combination with aspirin. We view this FDA decision as mildly disappointing, but manageable from a marketing standpoint.

Based on FDA concerns over possible COX-2 cardiovascular class effects, we also do not expect that the agency will grant Merck's Vioxx improved labeling during similarly scheduled meetings on Thursday.

While labeling improvement would have accelerated the current NSAID to COX-2 market conversion, we believe this FDA decision will not meaningfully impact our current growth forecasts for the Celebrex product line. Pharmacia remains a buy rated focus stock with a 12 month price target of $72.

Price 02/07/011	Target (12mo.)	Div.	Yield	Mkt.Value (MM)	52-Week Price Range
USD $56.13	$72	$0.48	0.9%	$73,923.2	33.75-64.00

	Annual EPS	Prev. EPS	Abs. P/E	Rel. P/E	EV/ EBITDA	EBITDA/ Share
12/01E	1.74		32.3X			
12/00E	1.44		39.0			
12/99A	1.11		50.6			

	March	June	Sept.	Dec.	FY End
2001E	0.39	0.53	0.37	0.41	Dec.
2000E	0.33	0.47	0.33	0.31	
1999A	0.26	0.40	0.21	0.24	

Total Debt (09/00)	$6.5bil
Common Shares	1,317
Est. 5-Yr EPS Growth	21%

1On 02/07/01 DJIA closed at 10,946.72 and S&P 500 at 1,340.89.
2Economic profit trend.

Pharmacia is a leading global pharmaceutical company created through the merger of Pharmacia & Upjohn with Monsanto Company and its G.D. Searle unit. Pharmacia has a broad production portfolio, a robust pipeline of new products , and an annual investment of more than $2 billion in pharmaceutical R&D.

Investment Summary

Celebrex: FDA Advisory Panel Recommends to Maintain Current Celebrex Labeling

The FDA's Arthritis Advisory Panel on Wednesday recommended no changes to Celebrex labeling after debating the possible safety advantages of this first generation COX-2 compared to two widely used non-steroidal anti-inflammatory drugs, diclofenac and ibuprofen.

Review of Celebrex CLASS Clinical Trial Findings and Sub-set Analysis

Celebrex is the only COX-2 specific inhibitor currently approved for osteoarthritis (OA) as well as adult rheumatoid arthritis (RA). In the CLASS (Celebrex Long-Term Arthritis Safety Study) clinical trial, Celebrex was evaluated in 8,000 patients in a comparison versus two widely used non-steroidal anti-inflammatory (NSAIDs) agents (ibuprofen and diclofenac).

Celebrex CLASS Clinical Trial Conducted at 2-4x Dosing Levels Against Comparable NSAIDS

Pharmacia structured the CLASS clinical trial to compare Celebrex to selective NSAIDS at dosing levels 2-4 times normal rheumatoid and osteoarthritis dosing levels (800 mg/day for Celebrex relative to normal 200 mg/day levels in osteoarthritis). The study was designed to measure the relative incidence of gastrointestinal bleeding related events, renal and hepatic toxicity as well as cardiovascular events (heart attacks, unstable angina against regularly used doses of selective NSAIDS.

The CLASS clinical study was complicated by the fact that Celebrex did not achieve statistical significance of its "primary" endpoint of ulcer complications (defined as bleeding ulcers, obstructions and perforations).

Celebrex achieved its "secondary" endpoint which was broader ulcer complications (bleeding users, obstructions and performations) combined with symptomatic ulcers, showing statistically significant superiority over NSAIDs evaluated in the study.

The CLASS clinical trial was also designed to mirror "real-world" use of NSAIDs in a broad osteoarthritis and rheumatoid arthritis patient population. As a result, the CLASS clinical trial did not exclude about 1,600 patients in the trial (20% of the studied patient population) taking low-dose aspirin.

This aspirin user base complicated the interpretation of clinical results with respect to cardioprotective effects and influence on both gastrointestinal and cardiovascular results. Importantly, Celebrex was not implicated in any thromboemboic or other cardiovascular events, such as edema or increased risk of heart attack or unstable angina.

Under sub-set analysis (excluding those patients on aspirin), Celebrex showed statistically significant benefit over NSAIDS on secondary endpoints when aspirin users were excluded from the evaluation.

Celebrex Shows Significant Statistical Improvement in Gastrointestinal Side

Effects Principally On the Non-Aspirin Ibuprofen Treatment Arm

The FDA's analysis of the secondary endpoint data indicated that Celebrex achieved statistical significance in its non-aspirin user treatment arm primarily over its advantages over ibuprofen. The agency voiced reluctance to provide differentiated labeling on just this single NSAID advantage, considering that there are currently nine different NSAIDS currently in use.

Aspirin Effects Complicate The Interpretation of the CLASS Study

The use of aspirin in the CLASS clinical trial also seemed to raise more questions than it answered. While Pharmacia contended that the use of aspirin tended to add to a higher rate of gastrointestinal complications, FDA reviewers believed that important cardioprotective effects tied to aspirin may be misrepresented or altered when combined, or eliminated in COX-2 therapy regimens. Reviewers generally called for further evaluation and study on this issue.

Net Result: Maintain Celebrex Label "Status Quo"

After nearly seven hours of discussions, the FDA panel decided that the current label for Celebrex appears to adequately describe relative gastrointestinal properties relative to NSAIDS. Reviewers voiced interest in studying further the use of aspirin and COX-2 inhibitors in combination, with perhaps some more specific labeling in the future on this issue.

Merck Vioxx Review Set For Thursday

Merck's Vioxx will undergo similar scrutiny on Thursday. Owing to the questions attached to Vioxx agenda asking whether further studies are warranted to ascertain cardiovascular risk differences between Vioxx and naproxen treatment groups in the VIGOR clinical trial, we expect that Vioxx's label will also be left unchanged. The VIGOR trial also excluded aspirin users , an apparent area of concern to the FDA.

Prescription Trends: COX-2 Inhibitors Remain In Dynamic Growth Mode

The overall COX-2 category posted a 21% increase in new prescriptions during the December, while the NSAIDs registered a 13% decline in new prescriptions for the month. Within the COX-2 inhibitors, Pharmacia/Pfizer's Celebrex continues to outperform Merck's Vioxx on a new prescription market share basis . In December, Celebrex captured 52% of the COX-2 market and 19.3% of the total COX-2/NSAIDs market. This compares to Vioxx at 48% of the COX-2 market and 19.1% of the total COX-2/NSAIDs market for December.

Since Vioxx was introduced in June of 1999, Celebrex has lost market share as Vioxx new prescriptions are growing at 40% in December, compared to 8% in new prescription growth for Celebrex.

Pharmacia's Valdecoxib NDA Filing Expected in Early 2001

We are expecting that Pharmacia's NDA for valdecoxib, the new second-generation COX-2 inhibitor, will be filed in early 2001. Based on increased COX-2 selectivity compared to existing agents, potent pain relief profile, rapid onset and prolonged once-daily dosing, valdecoxib is expected to increasingly penetrate more potent pain-control markets outside of traditional NSAIDS, such as medicinal narcotic, non-narcotic analgesic as well as other COX-2 inhibitors. Valdecoxib, is the same base agent as the Pharmacia-controlled injectable COX-2 inhibitor, parecoxib. Pharmacia is positioning parecoxib as a potential alternative to injectable Toradol (

ketorolac) as well as morphine in control applications. We are assuming an NDA filing for valdecoxib in early 2001 and commercialization in early 2002.

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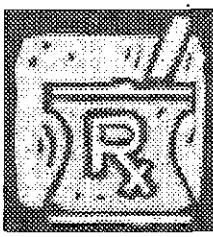
= = PHARMACIA = = PHA: BUY

EXHIBIT 186



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UBS Warburg

RESEARCH NOTE

February 8, 2001

Pharmaceuticals: Disappointing FDA Review of GI Safety Data for Celebrex

KEY POINTS

- Yesterday, Pharmacia (PHA-$56.13) presented data on Celebrex (copromoted with Pfizer) from the CLASS study to the FDA advisory committee. The panel rejected the company's claim that it is gentler on the stomach than the older nonsteroidal medications (NSAIDs) and recommended that the FDA deny Pharmacia's request for an improved label that would differentiate it from the older NSAIDs, which contain a warning for gastrointestinal toxicity.
- The FDA advisory committee will meet on Thursday, February 8th to review safety data for Merck's (MRK-$81.85) Vioxx. While we believe the data for Vioxx clearly demonstrates improved GI safety (which would give Vioxx a clear marketing advantage versus Celebrex), the study also resulted in statistically significantly higher adverse cardiac events for Vioxx than Naproxen (the comparator drug). While it is difficult to determine how the FDA and the advisory panel will handle these conflicting factors, we believe the most likely outcome is to leave the label essentially unchanged.
- While we view the FDA's review of both drugs and the panel's recommendation regarding Celebrex as disappointing, it is important to note that our forecasts for Celebrex and Vioxx are based on current prescription trends which are quite strong. Total prescriptions for Celebrex were up 16% in December and our 2001 U.S. revenue forcast is $2.55 billion, up 18%. Vioxx total prescriptions were up 77% in December and our 2001 U.S. revenue estimate is $2.3 billion, up 32%, which could actually prove to be conservative.
- We believed a positive FDA outcome could lead to upside in our model as improved labeling would facilitate stronger promotional efforts (DTC advertising) by the companies and would support the argument for better formulary position. Moreover, we expected that cleaner labels would have helped sustain growth for Celebrex and Vioxx, but not have caused a significant acceleration.
- While neither data set for Celebrex or Vioxx is perfectly clean, we believed that the data were positive on balance and the FDA panel would recommend improved labeling regarding gastrointestinal safety for both drugs. After yesterday's results, however, this appears unlikely.

DETAILS

Yesterday, Pharmacia presented data on Celebrex from the CLASS (Celecoxib Long-term Arthritis Safety Study) to the FDA advisory committee. The panel rejected the drug's claim that it is gentler on the stomach than the older nonsteroidal medications (NSAIDs) and recommended that the FDA deny Pharmacia's request for an improved label that would differentiate it from the older NSAIDs, which contain a warning for gastrointestinal toxicity. The FDA advisory committee will meet on Thursday, February 8th to review safety data for Merck's (MRK's) Vioxx.

Currently, the labels for both Celebrex and Vioxx carry warnings for GI side effects (bleeding, ulcerations and perforations of the stomach) similar to NSAIDs. Pharmacia and Merck both performed large studies to prove otherwise with intentions of having the FDA remove/improve the warning from their labels. The results of Pharmacia's CLASS study showed that Celebrex did not meet the primary endpoint of statistically significant reduction of non-symptomatic complicated ulcers. On the other hand, Merck's Vioxx did meet the primary endpoint of a statistically significant reduction in the risk of symptomatic ulcers and complicated GI events in the VIGOR (Vioxx Gastrointestinal Outcomes Research) trial. However other cardiac safety issues were uncovered. Importantly, these is not new data as both Pharmacia and Merck originally presented data from these studies in May 2000.

The table below summarizes the key points and findings of both studies. Importantly, the CLASS and VIGOR studies are not identical in design and should not be compared.

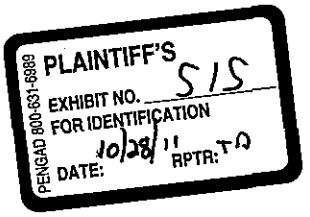

Exhibit 1

Parameter	VIGOR (n= 8076)	CLASS (n=7968)
Drug	Vioxx 50mg QD (2-4x max dose)	Celebrex 400mg BID (2-4x max dose)
Patients	RA	OA (73%); RA (27%)
Comparator	Naproxen 500mg BID	Ibuprofen 800mg TID Diclofenac 75mg BID
Low-dose aspirin	No	Yes (21%)
Duration	Median: 9 months Maximum: 13 months	6 months reported (median: 9 months; max: 13 months)
Primary Endpoint	4.5%/2.1% (p<0.001)	1.5%/0.8% (p=0.09)
Secondary Endpoint	1.4%/0.6% (p=0.005)	3.5%/2.1% (p=0.02)
Other Safety Measures	Rofecoxib showed increased incidence of edema and hypertension	

We believe that Celebrex and Vioxx are essentially equivalent and that while it is possible, it is highly unlikely that the FDA would grant one drug a preferential label versus the other. Therefore, we are not changing our revenue or earnings estimates. In fact, if prescription trends continue strong, our Vioxx forecast may prove to be conservative. The table below summarizes our U.S. and worldwide revenue assumptions for Merck and Pharmacia's COX-2 inhibitor products.

Additional information available upon request.

Exhibit 2

Sale Forecast for COX-2 Inhibitors

(Dollars in millions)

	Merck Vioxx/MK 663		Pharmacia/Pfizer Celebrex/valdecoxib	
	Sales	Growth	Sales	Growth
2001E				
U.S.	2,300	32%	2,550	18%
WW	3,025	40%	3,150	25%
2002E				
U.S.	2,700	18%	2,950	16%
WW	3,650	21%	3,725	18%

RISK FACTORS

Risks generally applicable to the pharmaceutical sector include: development risk (uncertainty regarding the timing, efficacy and market potential of new products), commercial risk (threats from new/existing competition, pricing pressures), regulatory risk (timing/status of approvals, changes in labeling or new warnings on existing products), patent risk (products losing patent protection may face significant market share/price erosion, potential litigation) and foreign exchange risk (due to the large base of non-U.S. sales for these companies).

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MORGAN STANLEY DEAN WITTER

Comment | Page 1

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United States of America

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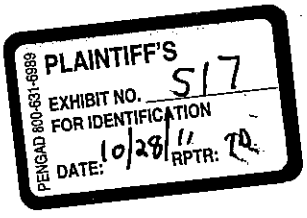
Company Update

April 18, 2000

Positive Results of Celebrex CLASS Trial Released

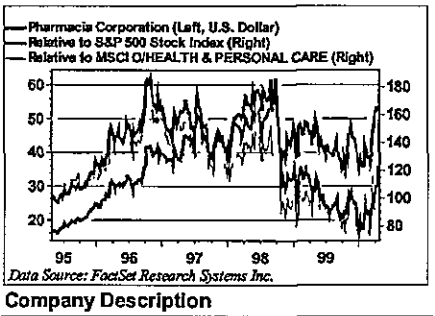
OUTPERFORM

Price (April 14, 2000):	$ 53.13
Price Target:	$65
52-Week Range:	$ 57.75 - 33.75



- **PHA and PFE announced positive results of the CLASS trial** In most respects, the study served its purpose of differentiating the long-term safety profile of Celebrex from NSAIDs.
- **Celebrex patients experienced fewer symptomatic ulcers** and ulcer complications than patients taking the comparator NSAIDs, ibuprofen and diclofenac.
- **Celebrex did not reach statistically significant superiority** on the primary endpoint of ulcer complications. However, excluding patients on aspirin, it was superior on both endpoints
- **PHA plans to submit these data to the FDA in 2Q00** in hopes of revising (or best case, removing) the GI warning that appears in the label. We forecast 2000 Celebrex sales of $2.4 bn

Price: Abs. and Rel. To Market & Industry



Company Description

Pharmacia Corporation is the result of a merger between Monsanto and Pharmacia Upjohn.

FY ending Dec 31:	1999A	2000E	2001E	2002E
EPS ($)	1.11	1.58	1.92	2.32
Prior EPS Ests. ($)	–	–	–	–
Consensus EPS Ests.($)	–	–	–	–
CEPS ($)	–	NA	NA	NA
P/E	47.9	33.6	27.7	22.9
P/E Rel. to (local index) (%)	–	–	–	–
P/CE	–	–	–	–
Price/Book	–	–	–	–
EV/EBITDA	–	17.7	–	–
Yield (%)	0.0	0.0	0.0	0.0

Market Cap ($ m)	66,659
Enterprise Value ($ m)	–
Debt/Cap (12/99)(%)	–
Return on Equity (12/99)(%)	–
L-T EPS Grth. ('yy - 'yy) (%)	NA
P/E to Growth	–
Shares Outstanding (m)	1,254.8

Q'trly EPS	1999A actual	2000E curr	2000E prior	2001E curr	2001E prior
Q1	–	–	–	–	–
Q2	–	–	–	–	–
Q3	–	–	–	–	–
Q4	–	–	–	–	–

E = Morgan Stanley Dean Witter Research estimate.

Please refer to important disclosures at the end of this report.

Positive Results of Celebrex CLASS Trial Released

Investment summary and conclusion:
On Monday before the market opened, PHA and PFE ($38) announced positive results of their eagerly anticipated CLASS study, which evaluated the incidence of serious gastrointestinal events of Celebrex versus leading NSAIDs, ibuprofen and diclofenac.

In most respects, the study served its purpose of differentiating the long-term safety profile of Celebrex from NSAIDs. OA and RA patients taking four times the recommended OA dose of the drug (800 mg/day) experienced fewer symptomatic gastrointestinal ulcers and ulcer complications than patients taking the other two drugs. The conclusion is confounded, however, by the fact that the trial did not demonstrate statistically significant superiority of Celebrex in the primary endpoint of ulcer complications, which includes bleeding ulcers, perforations and obstructions. However, on the second endpoint of ulcer complications *plus* symptomatic ulcers, Celebrex was shown to be statistically superior to the NSAIDs.

In addition to the GI system, the CLASS study evaluated Celebrex' safety in other major organ systems, including cardiovascular, renal and hepatic systems. Notably, Celebrex showed no increase in thromboembolic or other cardiovascular events — even among the subset of patients who did not take low-dose aspirin. Moreover, the drug demonstrated favorable differences with the NSAIDs on certain renal and hepatic endpoints.

PHA and PFE plan to submit these data to the FDA in hopes of revising (or best case, removing) the standard NSAID warning about GI events that currently appears in the label. A revision of the label is likely to have a positive impact on reimbursement and sales of Celebrex. We are making no change to our forecasts, as we had anticipated the study to corroborate the strong safety profile of the product. We are expecting 2000 sales of $2.4 billion and 2001 sales of $3.2 billion. MRK ($64 1/2) is also conducting long-term outcome studies of Vioxx (the VIGOR study). Though we have not yet seen the full data, MRK has reported the results are favorable and the company plans to file its sNDA with the FDA within the next couple of months.

Details of the Study
The CLASS Study (Celebrex Long-term Arthritis Safety Study) was a randomized, double-blind clinical outcomes trial conducted in approximately 8,000 patients with osteoarthritis and rheumatoid arthritis. Patients were randomized to one of three arms of the study, with about half on Celebrex (800 mg./day) and approximately 2,000 each on ibuprofen (2400 mg/day) and diclofenac (150 mg/day). Of the total, about 5,800 patients had osteoarthritis and the remaining 2,200 had rheumatoid arthritis.

The trial had two endpoints for evaluating the products' safety profile with respect to gastrointestinal events. The primary endpoint was "ulcer complications", which were defined as perforations, obstructions and GI bleeds. The second endpoint was "ulcer complication and symptomatic ulcers", which is broader in that it includes the events above in addition to symptomatic ulcers. Though the results numerically favored Celebrex for both of these endpoints, the primary endpoint of "ulcer complications" alone fell short of achieving statistical significance.

Incidence of "ulcer complications"	
NSAIDs	1.5%
Celebrex	0.7%
P value = 0.09	

Note: PHA reports that the difference was very close to achieving statistical significance. A difference of just two more events would have achieved a P value of 0.05.

The secondary endpoint which combines "ulcer complications" with symptomatic ulcers did demonstrate the statistical superiority of Celebrex versus ibuprofen and diclofenac.

Incidence of "ulcer complications" and symptomatic ulcers	
NSAIDs	3.5%
Celebrex	2.0%
P value = 0.03	

Subset analysis excluding patients on low-dose aspirin

In contrast to MRK's outcomes study for Vioxx (the VIGOR study), PHA did not exclude patients who were taking low-dose aspirin (up to 325 mg. per day). The results above are inclusive of the approximately 22% of patients in the study who were taking aspirin.

When a subset analysis is conducted to exclude the patients taking aspirin, Celebrex showed statistically signficant superiority over NSAIDs on *both* endpoints.

Incidence of "ulcer complications"	
NSAIDs	1.3%
Celebrex	0.4%
P value = 0.037	

Incidence of "ulcer complications" and symptomatic ulcers	
NSAIDs	3.0%
Celebrex	1.5%
P value = 0.02	

The more favorable results in the subset of patients that excluded low-dose aspirin use may be explained by the fact that aspirin is an independent risk factor for GI complications, which likely increased the incidence of "ulcer complications" in both the Celebrex and NSAID arms of the trial. The culpability of Celebrex in contributing to these severe GI events is called into question by the fact that in the non-aspirin subset of patients, the rate of "ulcer complications" in patients taking Celebrex alone is comparable to the background incidence in the general population.

Safety in Other Organ Systems

In addition to GI events, the CLASS study evaluated the comparative safety of Celebrex in the cardiovascular, renal, and hepatic systems. Notably, Celebrex showed no increase compared with NSAIDs in thromboembolic events (such as stroke or myocardial infarctions) or other cardiovascular events — even among the patients who were not taking low-dose aspirin.

Profile in the kidney and liver: The incidence of renal abnormalities and renal complications was significantly lower among Celebrex-treated patients than in those treated with diclofenac and ibuprofen. Additionally, fewer Celebrex patients developed hypertension or edema than those who were treated with ibuprofen. Patients on diclofenac developed more kidney and liver abnormalities than the patients in the Celebrex arm of the study.

Investment Thesis

PHA remains a favorite stock in our sector, with an Outperform rating. We estimate a 3 year CAGR of 20%, with potential upside from product sales such as Celebrex. While we are bullish on the COX-II inhibitor franchise, our models leave room for upside. Our 12 month price target is $65.

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Pharmacia Corp. - April 18, 2000

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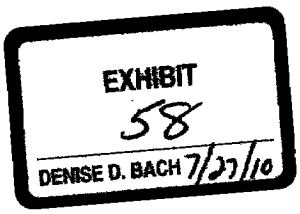
EXHIBIT 188

Time and Expense: Gerald A. Faich, MD, MPH



Bill To: Pfizer

PSA legal rates 675 hour for consultation, 725 for deposition

Rate $/hr
Project Number:

DATE	ACTIVITY	TIME	EXPENSE
12-Oct-06	review all paracoxib files	4	
13-Oct-06	meeting with Veisz --depo prep	5	20
17-Oct-06	depo prep 8-9am	1	
18-Oct-06	depo at 260 Broad 9-530	8.5	20
26-Oct-06	prep with Veisz	2.5	25
27-Oct-06	depo 815 to 330	7.25	25
22-Mar-07	Totals sent to H Veisz of 15.75 hours of deposition (@725 or $11,418) and		
	12.5 hours of preparation (@675 or $8437) and expense of $90 for parking		
	for total of $19,945		
11-May-07	RECEIVED $19,945		
8-May-07	prep of affidavit for summary judgment support several versions		
	and calls with Veisz	2	
12 to 24 aug	reconstruction of pfizer payments received and calls with Veisz on thi	1.5	
6-Sep-07	deposition preparation and various scheduling emails	2.5	25
7-Sep-07	deposition preparation	2	20
	deposition@725	1.5	